INDIAN AGRICULTURAL
RESEARCH INSTITUTE, NEW DELHI.

I. A. R. I. 6.
MGIPC—S4—10 AR—21-6-49—1,000.

CHEMICAL REVIEWS

EDITORIAL BOARD
W. ALBERT NOYES, JR., Editor
LOUISE KELLEY, Assistant Editor
H. F. JOHNSTONE C. S. HAMILTON
E. BRIGHT WILSON, JR. CARL F. CORI
N. H. FURMAN ROY C. NEWTON

VOLUME 43

25252
IARI

PUBLISHED BI-MONTHLY FOR
THE AMERICAN CHEMICAL SOCIETY
BY
THE WILLIAMS & WILKINS COMPANY
Baltimore, U. S. A.
1948

CONTENTS

Number 1, August, 1948

Structure and Synthesis of Cardiac Genins. Richard B. Turner........ 1
The Chemistry of 4-Hydroxyquinolines. Robert H. Reitsema.......... 43
Adsorption and Pore-Size Measurements on Charcoals and Whetlerites. P. H. Emmett.......... 69
The Chemical Reactions of Pentaerythritol and its Derivatives. S. F. Marrian.......... 149

Number 2, October, 1948

The Chemistry of the Organic Isocyanates. J. H. Saunders and R. J. Slocombe.......... 203
The Nature of the Glassy State and the Behavior of Liquids at Low Temperatures. Walter Kauzmann.......... 219
Liquid-Phase Alkylation of Aromatic Hydrocarbons. Alfred W. Francis 257
Brominations with *N*-Bromosuccinimide and Related Compounds. The Wohl–Ziegler Reaction. Carl Djerassi.......... 271
The Scattering of Light and its Applications to Chemistry. Gerald Oster 319

Number 3, December, 1948

On Doisynolic Acids, A New Class of Estrogens. K. Miescher.......... 367
Relationships between Absorption Spectra and Chemical Constitution of Organic Molecules. Lloyd N. Ferguson.......... 385
The Chemistry of the Phthalazines. Wyman R. Vaughan.......... 447
The Chemistry of Spiropyrans. Ahmed Mustafa.......... 509
Recent Developments in the Study of Hydrogen Overpotential. J. O'M. Bockris.......... 525

ERRATA

Vol. 41, Number 3, December, 1947

Page 445: For $p_{Cl_2} = 10^{-28}$ atm. read $p_{Cl_2} = 10^{-56}$ atm.
For $p_{H_2} = 4 \times 10^{-8}$ atm. read $p_{H_2} = 1.6 \times 10^{-5}$ atm.

Page 474: For

$$A = \frac{DD_0kTn_{0i}}{2\pi}$$

read

$$A^2 = \frac{DD_0kTn_{0i}}{2\pi}$$

STRUCTURE AND SYNTHESIS OF CARDIAC GENINS[1, 2]

RICHARD B. TURNER

Department of Chemistry, Harvard University, Cambridge, Massachusetts

Received December 9, 1947

CONTENTS

I. Introduction 1
II. Stereochemistry 2
  A. Digoxigenin and digitoxigenin 2
  B. Thevetigenin and uzarigenin 5
  C. Gitoxigenin 6
  D. Strophanthidin and periplogenin 8
  E. Allostrophanthidin and alloperiplogenin 13
III. Glycoside cleavage 13
IV. Genins and glycosides of indefinite structure 15
  A. Ouabagenin 15
  B. Sarmentogenin 16
  C. Adynerigenin and neriantogenin 16
  D. Scillaren A and scilliroside 18
  E. Hellebrin 18
  F. Diginin 20
V. Miscellaneous glycosides 21
  A. New glycosides 21
    1. Somalin 21
    2. Adonitoxin 21
    3. Cymarol 22
    4. Convalloside 22
    5. Cheirotoxin 23
    6. Sarmentoside A and sarmentoside B 23
  B. Synthetic glycosides from natural genins 23
VI. Synthesis of cardiac genins 23
  A. Lactone side chain 23
  B. C_{14}-hydroxyl group 29
  C. C_5-hydroxyl group 35
VII. References 38

I. INTRODUCTION

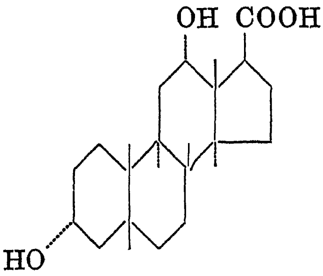
The stereochemistry and partial synthesis of the cardiac genins have been actively investigated during the past several years. In the course of this work a number of genins have been degraded to derivatives of etiodesoxycholic acid (I), the spatial configuration of which has been firmly established by the recent work of Reichstein (158), Gallagher (25), and Kendall (84).[3] In many instances,

---

[1] This paper was presented at the Symposium on Steroidal Compounds which was held under the auspices of the Division of Medicinal Chemistry at the 112th Meeting of the American Chemical Society, New York City, September 18, 1947.

[2] Previous reviews are included in references 15, 39, 49, 71, 124, 145, 151, 175, and 176.

[3] The stereochemistry of desoxycholic acid and its derivatives has recently been reviewed by Shoppee (152). The dotted and solid lines in formula I refer respectively to α- and β-orientations, which are used in the sense suggested by Fieser (19c).



I
Etiodesoxycholic acid

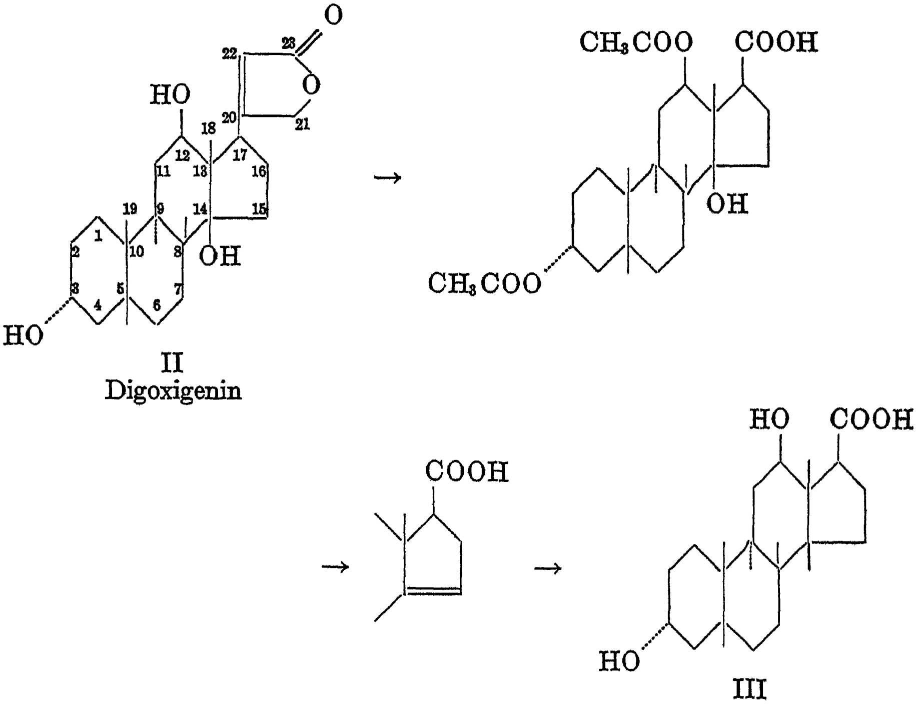
therefore, it is now possible to relate the cardiac genins to known reference compounds. The synthesis of important degradation products in this series has confirmed formulas assigned on the basis of other evidence, and in addition several compounds have been prepared that are closely related to the natural aglycones.

The pertinent literature up to and including that for the year 1947 is reviewed in the present paper. A few allied topics of special interest have also been included.

II. STEREOCHEMISTRY

A. DIGOXIGENIN AND DIGITOXIGENIN

In 1938 Steiger and Reichstein (163) degraded the aglycone digoxigenin (II) by a series of steps involving acetylation, oxidation with potassium perman-

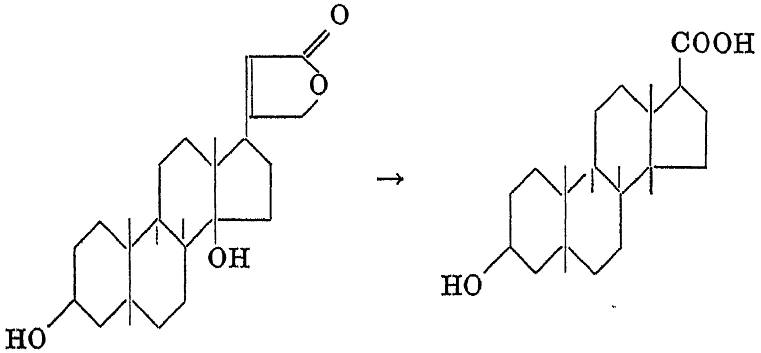


II
Digoxigenin

III
12-Epietiodesoxycholic acid

ganate, dehydration, and hydrogenation to an acid that was subsequently identified as 12-epietiodesoxycholic acid (III) by Mason and Hoehn (83). This evidence establishes the location and orientation (3(α), 12(β)) of the two secondary hydroxyl groups of the genin, the configuration of the nucleus at all centers of asymmetry except that at C_{14}, and the position (C_{17}) and configuration (β) of the lactone side chain.[4]

In a similar manner Hunziker and Reichstein (36) converted digitoxigenin (IV) into 3(β)-hydroxyetiocholanic acid (V), and thereby proved the incorrectness of the view held previously that digitoxigenin was a 3(α)-hydroxy compound (19a, 76).



IV Digitoxigenin

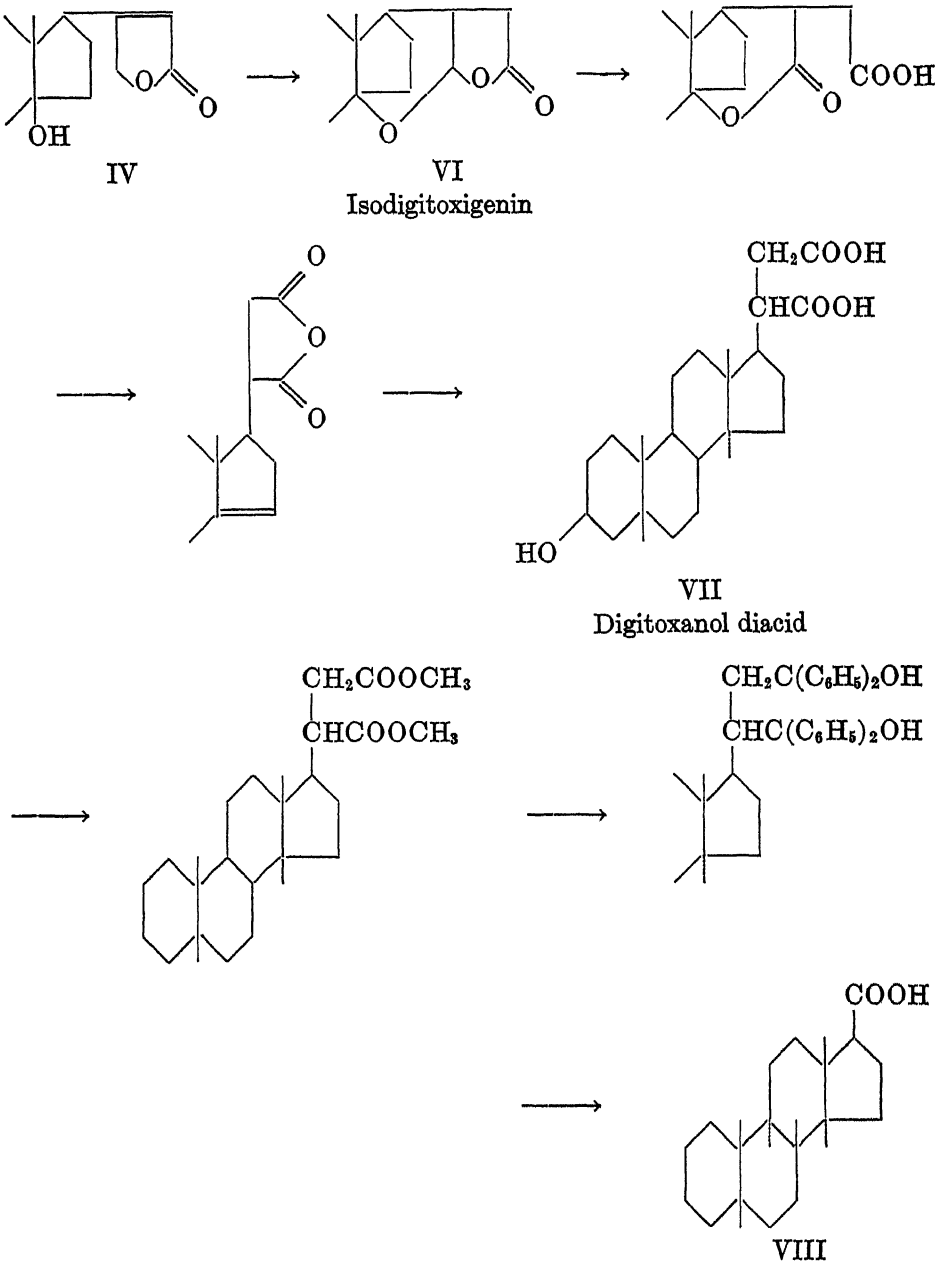
V 3(β)-Hydroxyetiocholanic acid

Inasmuch as the degradations just described offer an opportunity for inversion of the configuration at C_{14}, it cannot be inferred that the genins, like the bile acids, possess a *trans* junction between rings C and D. It can in fact be shown that in this respect the cardiac aglycones are unique and differ from other naturally occurring steroids in the presence of a *cis* C/D ring fusion.

When digitoxigenin is allowed to stand with cold methanolic potassium hydroxide, it undergoes an irreversible isomerization to isodigitoxigenin (VI) (55). This reaction is typical of the cardiac glycosides as well as of the aglycones. It is evident that the formation of the bicyclic isogenin VI is possible only if the hydroxyl group at C_{14} and the lactone side chain at C_{17} are *cis* in digitoxigenin (IV), or if a *cis* arrangement can be attained by inversion at either of these points under the conditions of the reaction. By a series of transformations (VI → VIII) not involving the asymmetric center at C_{17}, the isogenin has been converted into etiocholanic acid (VIII) (49, 57), for which the 17(β)-configuration has been established. The identity of digitoxigenin and isodigitoxigenin with respect to their orientations at C_{17} therefore excludes the possibility of an inversion at this point, which might result from an intermediate β,γ-shift of the lactone double bond to $C_{17}{:}C_{20}$. Under the mild conditions employed for the

---

[4] The double bond of the lactone ring was originally assigned to the β,γ-position by Jacobs (60) on the basis of analogous color reactions (Legal test) obtained with the genins and with the β,γ-angelica lactones. More recent evidence derived by Elderfield (96) from ultraviolet absorption studies and hydrogenation experiments indicates that the substances are α,β-unsaturated lactones.



IV

VI
Isodigitoxigenin

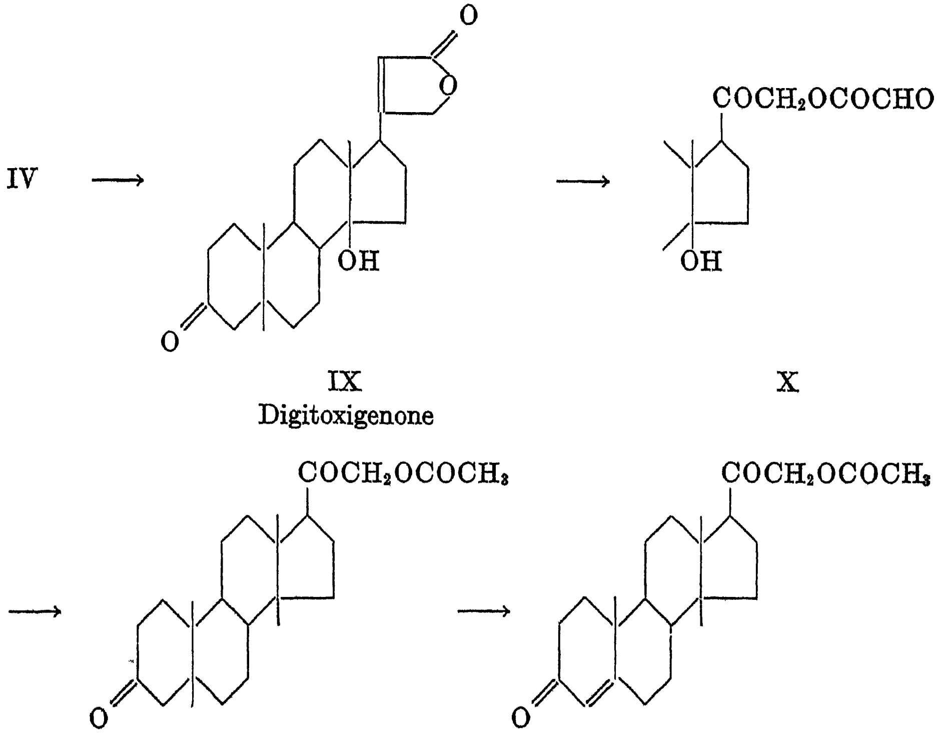
VII
Digitoxanol diacid

VIII
Etiocholanic acid

preparation of VI, epimerization at C_{14} is unlikely, and on the basis of this assumption it follows that the groups in question are *cis* in digitoxigenin. The β-configuration can, therefore, be assigned to the C_{14}-hydroxyl group, an arrangement which requires a *cis* junction between rings C and D. This conclusion is supported by the formation of cyclic keto lactones ($C_{21} \rightarrow C_{14}$) from strophanthidin (5, 12, 16, 37) and digitoxigenin (36, 88),[4a] and by the synthesis of methyl 3(β)-acetoxy-14(β)-hydroxyetiocholanate (CX) (page 33), which has been obtained as a degradation product of digitoxigenin.

Similar arguments can be advanced in the case of other members of the group, and the formulations of digoxigenin (II) and digitoxigenin (IV) are in all probability correct.

The interesting conversion of digitoxigenin into desoxycorticosterone acetate (XII) has recently been reported by Meyer and Reichstein (90). Careful oxidation of IV with chromic acid gives digitoxigenone (IX), which on ozonolysis suffers a rupture of the lactone ring. The intermediate glyoxalate (X) has not been isolated in this case but is converted by standard procedures (hydrolysis, acetylation, etc.) into 21-acetoxypregnane-3,20-dione (XI), identified by comparison with an authentic sample. The transformation of XI into desoxycorticosterone acetate was accomplished earlier by Reichstein and Fuchs (120).



IX
Digitoxigenone

X

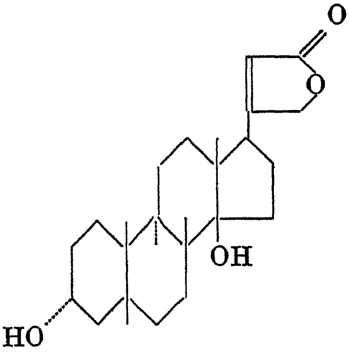
XI

XII

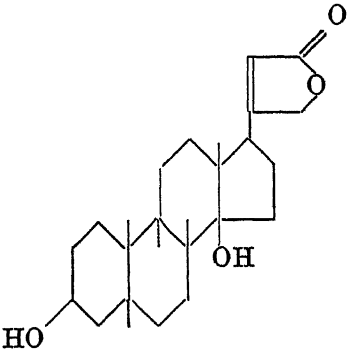
B. THEVETIGENIN AND UZARIGENIN

A crystalline glycoside, thevetin, was isolated from natural sources in 1933 by Chen and Chen (7). On treatment with alkali the glycoside gives an iso compound analogous to that derived from digitoxigenin, and for this reason the presence of a hydroxyl group at C_{14} in thevetin is assumed. The hydrolytic conditions required for the preparation of the aglycone, however, are so severe that this hydroxyl group is lost, and only a dehydration product, anhydrothevetigenin, can be isolated. The anhydro compound differs from Δ^{14}-anhydrodigitoxigenin, but on oxidation both compounds yield the same 3-keto derivative, anhydrodigitoxigenone (179). The true aglycone thevetigenin is therefore probably the C_3-epimer of digitoxigenin and is assigned formula XIII.[5]

[4a] *Added to proof, July 17, 1948:* This evidence is discussed in a recent paper by Buzas and Reichstein (5a), which appeared too late for inclusion in the present manuscript.



XIII
Thevetigenin



XIV
Uzarigenin

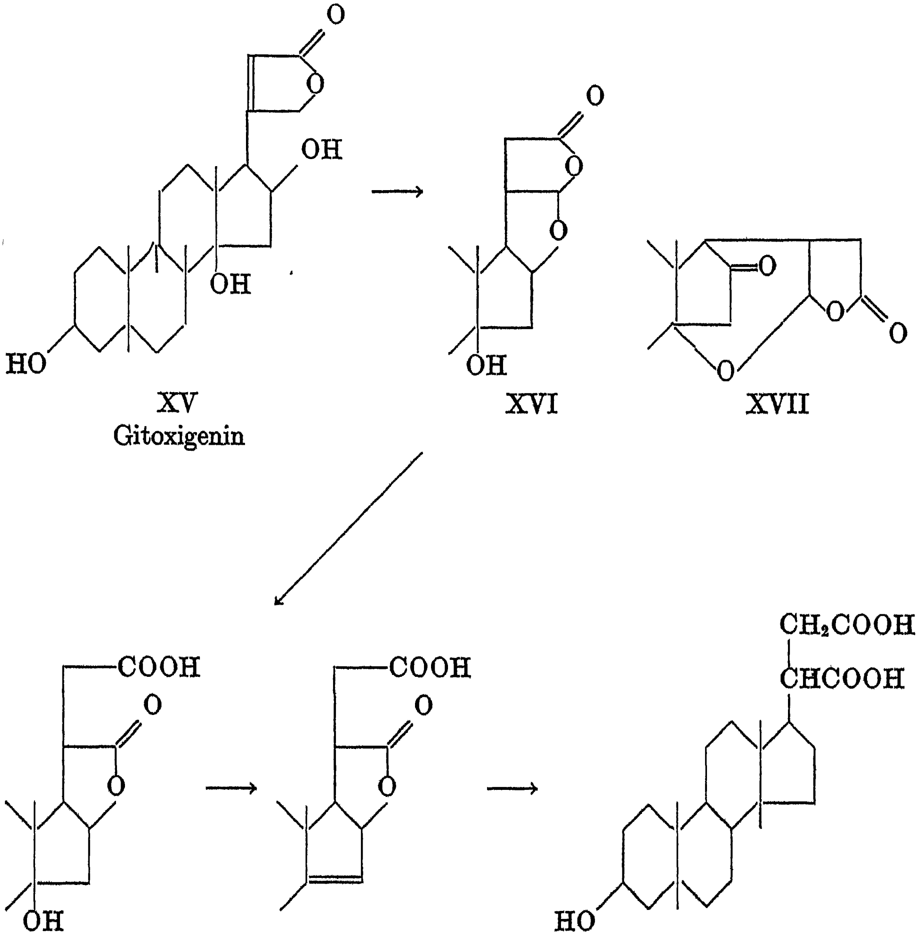
Isomeric with digitoxigenin and thevetigenin is the aglycone uzarigenin, which occurs in combination with two molecules of glucose as the glucoside uzarin (195). As in the case of thevetin, hydrolytic elimination of the sugar component is accompanied by loss of the tertiary hydroxyl group, and only anhydro derivatives of the true aglycone have been obtained (174, 178). In addition to the main product, α-anhydrouzarigenin, to which a Δ^{14}-structure has been assigned, a small amount of an isomer, β-anhydrouzarigenin, has been isolated for which Tschesche proposed the alternate $\Delta^{8,14}$-formulation. The latter point has not been established. Hydrogenation of the α-isomer proceeds smoothly with the absorption of 2 moles of hydrogen, and gives a mixture from which two completely saturated lactones can be isolated. These compounds, α_1- and α_2-tetrahydroanhydrouzarigenins, differ with respect to their configurations at the new center of asymmetry C_{20}, but both on degradation furnish etioallocholanic acid in which the A/B ring fusion is of the *trans* type (175, 176, 177). Uzarigenin, therefore, belongs to the cholestane series and it is the only genin thus far encountered for which this arrangement has been demonstrated. The β-orientation of the C_3-hydroxyl group is probable (see page 25) and formula XIV has accordingly been proposed for the unaltered genin (*cf.* 133).

C. GITOXIGENIN

The aglycone gitoxigenin (XV) is distinguished from other genins by the presence of a secondary hydroxyl group at C_{16} (48, 56). On treatment with alkali the unsaturated lactone ring reacts with this hydroxyl group in preference to the one at C_{14} and gives an isogenin (XVI) containing a stable five-membered ring. After oxidation of gitoxigenin to a 16-keto derivative, interaction of the lactone side chain with the hydroxyl group at C_{14} is observed. Gitoxigenin, therefore, can form two types of iso compounds (XVI and XVII) that involve the C_{16}-hydroxyl group on the one hand and the C_{14}-hydroxyl group on the other.

---

[5] In this connection it should be mentioned that the behavior of anhydrothevetigenin and digitoxigenin toward digitonin is anomalous. Of the two substances only the 3(α)-derivative, anhydrothevetigenin, affords an insoluble digitonide. This test as applied to the cardiac genins is therefore of doubtful value. Further examples of the reaction of the aglycones with digitonin are listed on page 2256 of reference 178.



XV
Gitoxigenin

XVI

XVII

XVIII

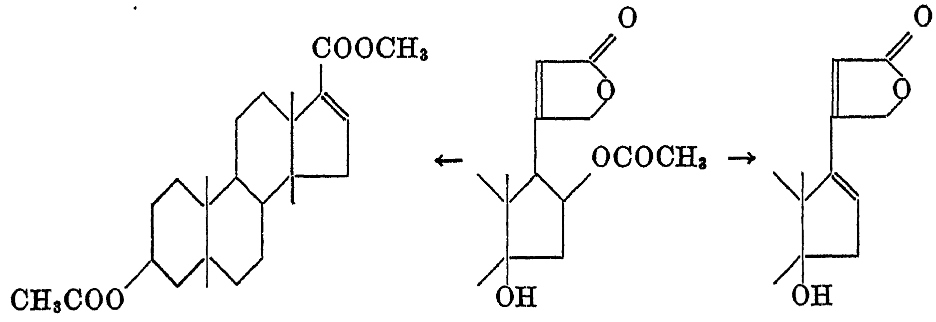
XIX

VII
Digitoxanol diacid

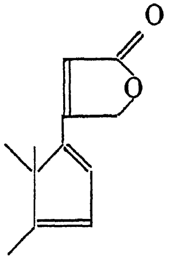
This behavior has been interpreted as evidence for the *cis* arrangement of the substituents at C_{14}, C_{16}, and C_{17} (151).

The β-orientation at C_{17} as well as at C_3 is demonstrated by the conversion of XVI into digitoxanol diacid (VII) (57). This transformation is accomplished by hypobromite oxidation of the isogenin to isogitoxigenic acid (XVIII), which in turn affords the anhydro acid XIX on dehydration. Hydrogenation of the latter compound is accompanied by hydrogenolysis at C_{16} and gives the dicarboxylic acid VII, obtained also from digitoxigenin (57).

Gitoxigenin yields a 3,16-diacetate (XX), which has recently been degraded to methyl 3(β)-acetoxy-Δ^{16}-etiocholenate (XXI) (86). This product was identified by comparison with a sample prepared from 3(β)-acetoxy-17-etiocholanone by way of the cyanohydrin and unsaturated nitrile (86, 122).



XXI XX XXII



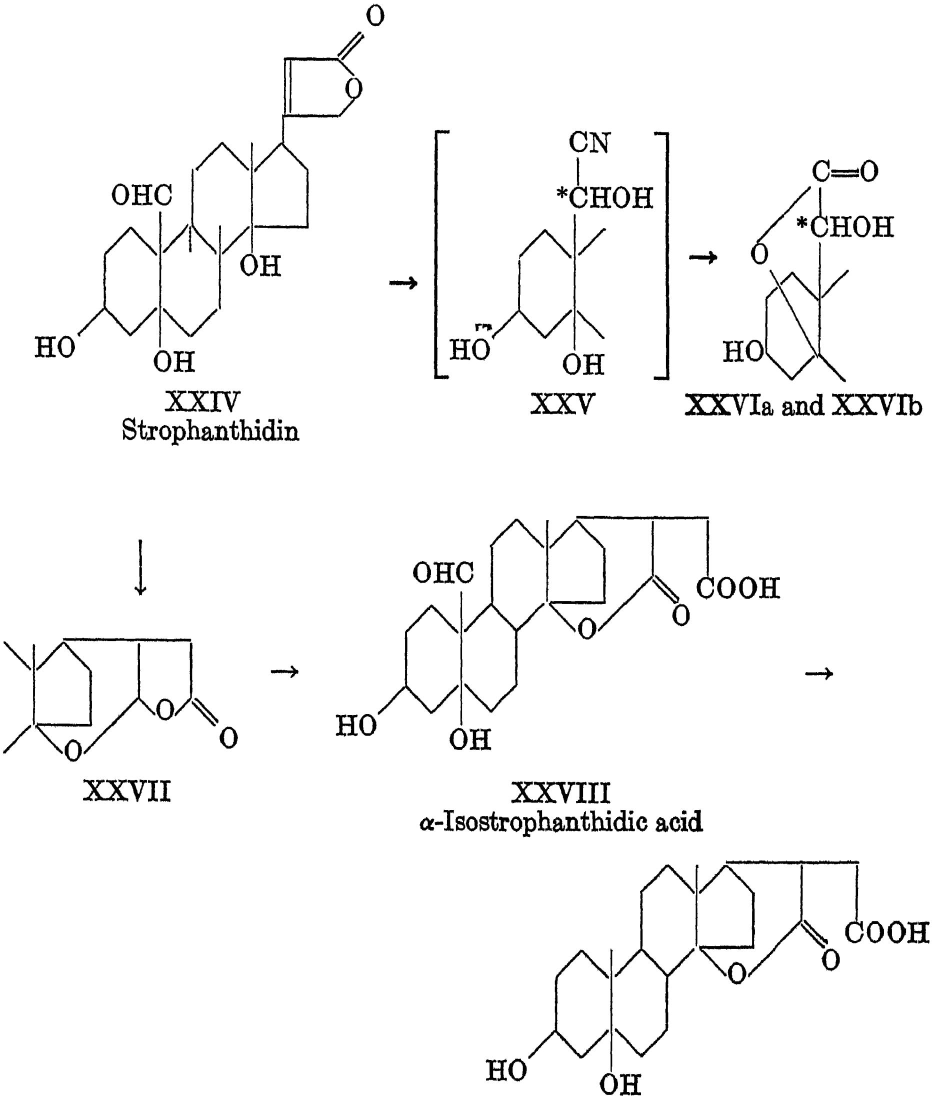
XXIII

One molecule of acetic acid is easily eliminated from gitoxigenin diacetate (XX) when this substance is chromatographed on alumina. There can be isolated a doubly unsaturated lactone, monoanhydrogitoxigenin (XXII), which shows characteristic absorption in the ultraviolet at 273 mμ, log ϵ = 4.4 (85). A dianhydro derivative (XXIII) of gitoxigenin has also been prepared (197), which absorbs maximally at about 337 mμ, log ϵ = 4.7 (180).

D. STROPHANTHIDIN AND PERIPLOGENIN

Certain of the cardiac aglycones, e.g., strophanthidin and periplogenin, possess in addition to the tertiary hydroxyl group at C_{14} a second tertiary hydroxyl group at C_5 (53). The *cis* relation between this substituent and the angular group at C_{10} was established by Jacobs and Elderfield (51), and is based on the following facts.

Strophanthidin (XXIV) on catalytic hydrogenation absorbs 1 mole of hydrogen and gives dihydrostrophanthidin containing a saturated lactone side chain. Under the conditions of reduction the C_{10}-aldehyde group is not attacked. The reaction of the dihydro compound with potassium cyanide affords a mixture of isomeric cyanohydrins (XXV) which has not been resolved, but which yields two homolactones (XXVIa and XXVIb) on hydrolysis with acetic acid. These substances are epimeric at C_{19} and on careful oxidation both compounds give the same 3,19-diketohomolactone.



XXIV
Strophanthidin

XXV

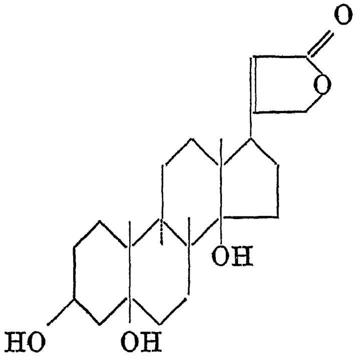
XXVIa and XXVIb

XXVII

XXVIII
α-Isostrophanthidic acid

XXIX
α-Isoperiplogenic acid

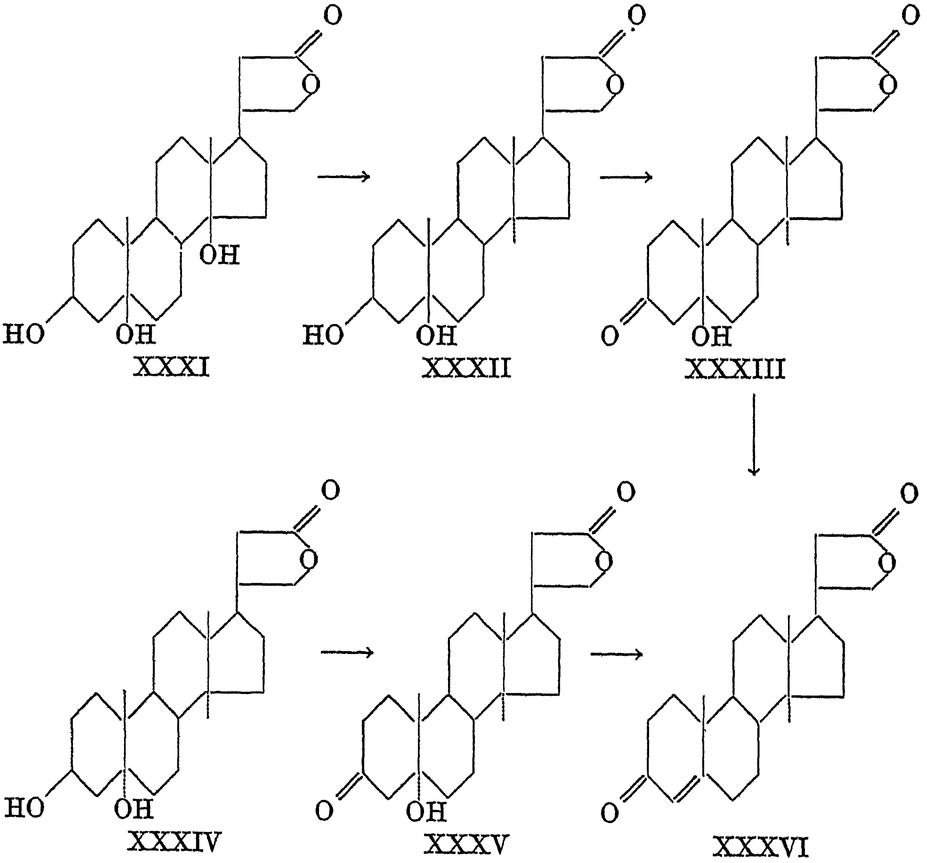
Strophanthidin when treated with alkali forms an iso compound (XXVII), which can be converted into α-isostrophanthidic acid (XXVIII) (44). Reduction of the angular aldehyde group (45) by the Wolff–Kishner procedure affords α-isoperiplogenic acid (XXIX), obtained also from periplogenin (XXX) (52). This iso acid (XXIX) has been related through a common derivative to



XXX

digitoxigenin (46), which in turn has been degraded to etiocholanic acid as noted previously.

It can be concluded then that the angular groups at C_{10} in strophanthidin and periplogenin occupy the same spatial position (β) as does the C_{10}-methyl group of the bile acids. If the possibility of rearrangements during the Wolff–Kishner reaction is excluded, the two aglycones must be 5(β)-hydroxy compounds differing only in the nature of the groups attached at C_{10}.

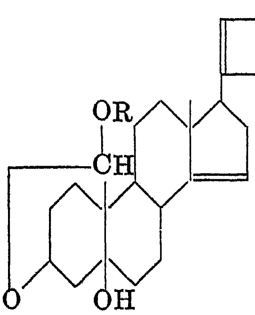


XXXI XXXII XXXIII

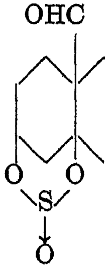
XXXIV XXXV XXXVI

The orientation at C_5 has been explored further by Plattner, Segre, and Ernst (114). Dihydrostrophanthidin was subjected to Wolff–Kishner reduction, and a product was obtained that is identical in all respects with dihydroperiplogenin (XXXXI). Dehydration and hydrogenation of XXXXI furnish a 14-desoxy derivative (XXXXII) that differs from a related synthetic product (XXXXIV) of known structure (see page 37). The difference persists in the 3-keto derivatives XXXXIII and XXXXV, but on elimination of the asymmetry at C_5 both compounds give the same α,β-unsaturated ketone (XXXXVI). It follows that XXXXIII and XXXXV are C_5-epimers and since the $5(\alpha)$-configuration of the latter is known, the corresponding $5(\beta)$-orientation can be assigned to XXXXIII.

For the C_3-hydroxyl groups in strophanthidin and periplogenin, the β-configuration is inferred from the following observations. Strophanthidin with alcoholic hydrogen chloride yields an anhydro derivative, which no longer possesses the aldehydic or secondary hydroxylic functions of the original aglycone. For this substance the cyclic lactol structure XXXVII has been proposed (43). Such a transformation would appear to be possible only if the hydroxyl group at C_3 is in the β-position (i.e., *cis* to the C_{10} aldehyde group).[6]



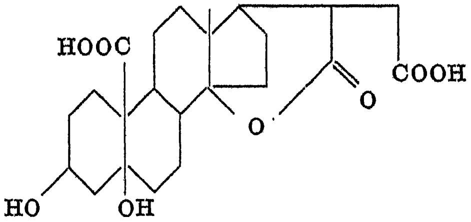
XXXVII



XXXIX

---

[6] Certain abnormalities in the behavior of α-isostrophanthic acid (XXXVIII) were noted by Jacobs and Gustus (54), who reported that the substance does not form a lactone. A lactone is readily obtained, however, from an isomeride, β-isostrophanthic acid, which has been variously described as the C_3- or C_5-epimer of XXXVIII (15, 182). No adequate explanation of these results has been advanced.



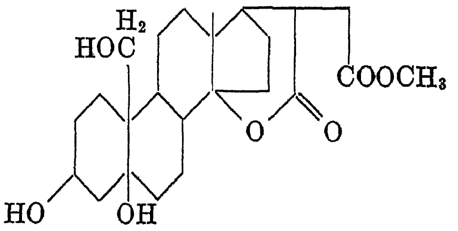
XXXVIII

A *cis* relation between the hydroxyl substituents at C_3 and C_5 is likewise implied by the formation of neutral sulfites (partial formula XXXIX) from α-isostrophanthidic acid (52; *cf.* 47, 50) and from strophanthidin (73, 114) by the action of thionyl chloride. A neutral carbonate of similar constitution has also been obtained from a degradation product of periplogenin by treatment with phosgene and pyridine (159).

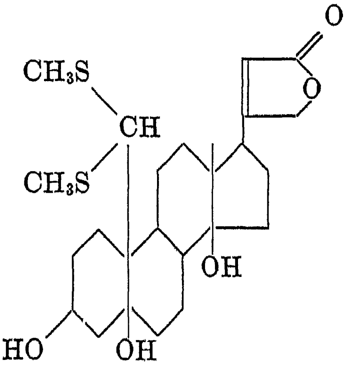
Conclusive evidence for the β-orientation at C_3 in periplogenin has recently been provided by Speiser and Reichstein (159), who succeeded in degrading periplogenin acetate to methyl 3(β)-acetoxyetioallocholanate (128, 161). On the basis of this work and in view of the evidence that has already been given, a similar arrangement at C_3 is probable in strophanthidin.

Arguments for the configuration of strophanthidin based on its conversion into derivatives of periplogenin are weakened to some extent by the fact that rearrangements under the conditions of the Wolff–Kishner reduction are not rigorously excluded. The classical conversions of coprosterol into epicoprosterol and of epidihydrocholesterol into dihydrocholesterol under the influence of sodium alkoxides at high temperature (198) serve to illustrate this point. A search has therefore been made for milder conditions for the conversion of strophanthidin into products of known structure.

In 1931 Jacobs and his associates (52) treated α-isostrophanthidolic acid methyl ester (XL) and its 3-acetate with phosphorus halides, thionyl chloride, and various halogen acids in the hope of replacing the primary hydroxyl group at C_{19}. In no case could this be accomplished. More recently Koechlin and Reichstein (69) prepared the methylsulfonyl derivative of methyl 19-hydroxyetioallocholanate, obtained by a series of reactions starting with strophanthidol acetate (*cf.* LXIII). Only products resulting from a rearrangement of the neopentyl system could be obtained from the reaction of this substance with sodium iodide.



XL



XLI

By treatment of strophanthidin with methyl mercaptan in the presence of zinc chloride a mercaptol (XLI) is obtained (69), which should be susceptible to desulfuration with Raney nickel (92). The results of this work are not available at the present time.

A number of other transformations of strophanthidin have been carried out by Ehrenstein (12) and Ehrenstein and Johnson (13).

E. ALLOSTROPHANTHIDIN AND ALLOPERIPLOGENIN

Of considerable stereochemical interest are the inactive glycosides allocymarin (38), alloemicymarin (41, 72), and alloperiplocymarin (64), which have been isolated from plant material after prolonged storage. These substances are isomeric with cymarin (strophanthidin-cymarose), emicymarin (periplogenin-digitalose), and periplocymarin (periplogenin-cymarose), respectively, and are apparently derived from these glycosides by the action of enzymes. Lamb and Smith (72) were able to obtain alloemicymarin by treatment of pure emicymarin with a crude enzyme preparation from the seeds of *Strophanthus emini*.

Jacobs (38) found that the isomerism involves the aglycone portion of cymarin, for cymarose is obtained on hydrolysis of both the active and inactive glycosides. The genin isolated from the latter, however, is not identical with strophanthidin and is therefore called allostrophanthidin. Further investigation of this material by Bloch and Elderfield (2) has revealed the fact that the asymmetric centers at C_3 and C_5 are not responsible for the observed difference; the ultraviolet absorption spectra of alloemicymarin and alloperiplogenin exclude the possibility of isomerism in these compounds based on a shift of the lactone double bond (64).

Allostrophanthidin, in contrast to strophanthidin, does not yield an isogenin on treatment with alkali (38), and Tschesche and his collaborators (184) observed the failure of alloemicymarin to furnish an iso compound under similar conditions. On the basis of this evidence it was proposed that the allogenins differ from their normal counterparts in a *trans* arrangement of the C_{14}-hydroxyl group and the lactone side chain. Such an arrangement could be attained by inversion at C_{14}, an assumption originally favored by Bloch and Elderfield, or by a corresponding inversion at C_{17}. The latter explanation is preferred by Tschesche (184) and by Katz and Reichstein (64), for the isomerism persists in trianhydroalloperiplogenin in which all three hydroxyl groups have been removed by dehydration. The correctness of this view was subsequently established by Speiser and Reichstein (159) by the degradation of alloperiplogenin to methyl 3(β)-acetoxy-14-iso-17-isoetioallocholanate (CI) and to methyl 14-iso-17-isoetioallocholanate, which possess the α-configuration at C_{17} (112).[7]

III. GLYCOSIDE CLEAVAGE

An outstanding difficulty in the elucidation of the structures of certain genins has been presented by the extreme difficulty with which glucose, rhamnose, and digitalose (119) are eliminated when attached directly to the steroid nucleus.

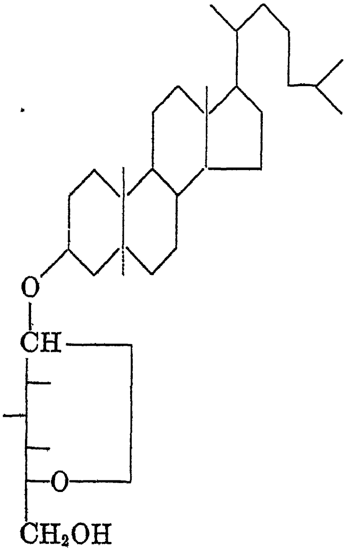
---

[7] The structure of these compounds is discussed in a later section (page 30).

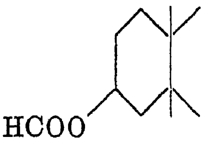
This behavior contrasts with the easy rupture of steroid–carbohydrate linkages that involve the 2-desoxysugars cymarose and digitoxose. Thus thevetin (2 glucose, digitalose?), uzarin (2 glucose), emicymarin (digitalose), alloemicymarin (digitalose), ouabain (rhamnose), and convallatoxin (rhamnose) require hydrolytic conditions so drastic that the aglycones undergo partial anhydrization.

In 1942 Mannich and Siewert (78) introduced a particularly mild method of cleavage and for the first time obtained from ouabain the unaltered aglycone ouabagenin. The method consists in treatment of ouabain with cold acetone containing a small amount of hydrogen chloride, under which conditions the glycoside dissolves as its monoacetone derivative. During the space of 2 or 3 weeks rhamnose is split off as the acetonide of a chloro sugar and ouabagenin acetonide crystallizes in good yield, accompanied by only small amounts of an anhydro derivative. The free genin is readily obtained by treatment of the acetone derivative with very dilute mineral acid. Other ketones, e.g., butanone and cyclohexanone, have been substituted for acetone in this reaction.

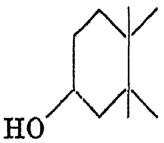
Employing Mannich's procedure, Reichstein and Katz (121) split convallatoxin into rhamnose and strophanthidin. This work provides proof for the formula first suggested for this glycoside by Fieser and Jacobsen (20), who showed that the convallatoxigenin benzoate of Tschesche and Haupt (186) is identical with anhydrostrophanthidin benzoate (43). The splitting of digitalose from emicymarin and alloemicymarin has also been effected by the method of Mannich (65).



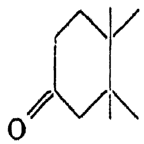
XLII



XLIII



XLIV



XLV

Unfortunately, in certain cases the cleavage employed with such success above gives poor yields or fails completely. This phenomenon has been observed particularly with glycosides that are very difficultly soluble in acetone. Accordingly, Steinegger and Katz (164) investigated the possibility of an oxidative degradation of the sugar moiety in the hope of obtaining more easily hydrolyzable products. Such an approach was suggested by the conversion of bornyl glucuronide into bornyl formate by the action of periodic acid (35). β-(Cholestanyl)-*d*-glucoside-1,5 (XLII) and the corresponding glucoside of androsterone were used as model compounds, and although periodic acid proved unsatisfactory, it was found that by the use of chromic acid at 18°C. three products can be isolated which have been identified as cholestanyl formate (XLIII), cholestanol (XLIV), and cholestanone (XLV). In addition a small acidic fraction is obtained which yields further amounts of cholestanol on saponification. Analogous results are obtained for the androsterone glucoside, and in this case mild alkaline hydrolysis of the crude oxidation product followed by a second treatment with chromic acid affords a 50 per cent yield of pure 3,17-androstanedione.

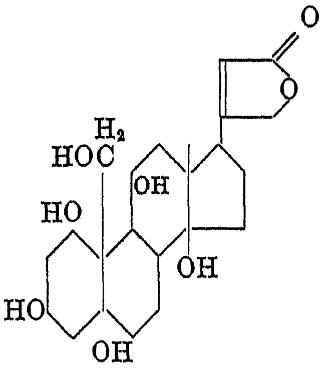
IV. GENINS AND GLYCOSIDES OF INDEFINITE STRUCTURE

A. OUABAGENIN

The results of the investigation of ouabagenin have been reviewed elsewhere (124) and are reproduced here only in outline.

Of the eight oxygen atoms present in the aglycone, two are presumably associated with the lactone side chain; one is evidently present as a tertiary hydroxyl group at C_{14}, since ouabain on treatment with alkali gives isoöuabain (40). Of the remaining five hydroxyl groups, four are readily acetylated. The fifth is therefore assumed to be tertiary and has been assigned to C_5 by analogy with strophanthidin and periplogenin.

Acetolysis of ouabain proceeds with the loss of formaldehyde (42), and for this reason a hydroxyl group has been assigned to C_{19}. Ouabagenin does not react with lead tetraacetate and thus contains no adjacent hydroxyl groups (78). The monoacetone derivative is therefore assumed to involve α,γ-hydroxyl groups, which must be *cis* on the basis of this interpretation. These groups



XLVI
Ouabagenin
(Mannich and Siewert, 1942)

have been placed provisionally at C_1 and C_3. The remaining hydroxyl group has been tentatively assigned to C_{11} (21, 79, 187) and is probably α-oriented if the proposal regarding its position is correct, since it is readily acetylated (*cf.* 26).

The foregoing evidence led Mannich and Siewert (78) to propose XLVI as the formula of ouabagenin.

B. SARMENTOGENIN

The aglycone sarmentogenin, obtained by Jacobs and Heidelberger (58) from the glycoside sarmentocymarin, is an isomer of digoxigenin. One of the two secondary hydroxyl groups is located at C_3 (183) and the other has been placed at C_{11} by reason of its hindered character. The latter proposal has not been substantiated, however, and is not favored by Reichstein (124) in view of certain abnormalities in specific rotation. The possibility that sarmentogenin might be a 3,12-dihydroxy compound epimeric with digoxigenin has been carefully tested by Katz and Reichstein (64), who prepared the diketo derivative sarmentogenone. This product is not identical with digoxigenone (156), and the structure of sarmentogenin must therefore be regarded as uncertain.[7a]

C. ADYNERIGENIN AND NERIANTOGENIN

An interesting structural problem is presented by the aglycones adynerigenin and neriantogenin, which have been isolated in small amounts from oleander leaves as the inactive glycosides adynerin (94) and neriantin (146, 185).

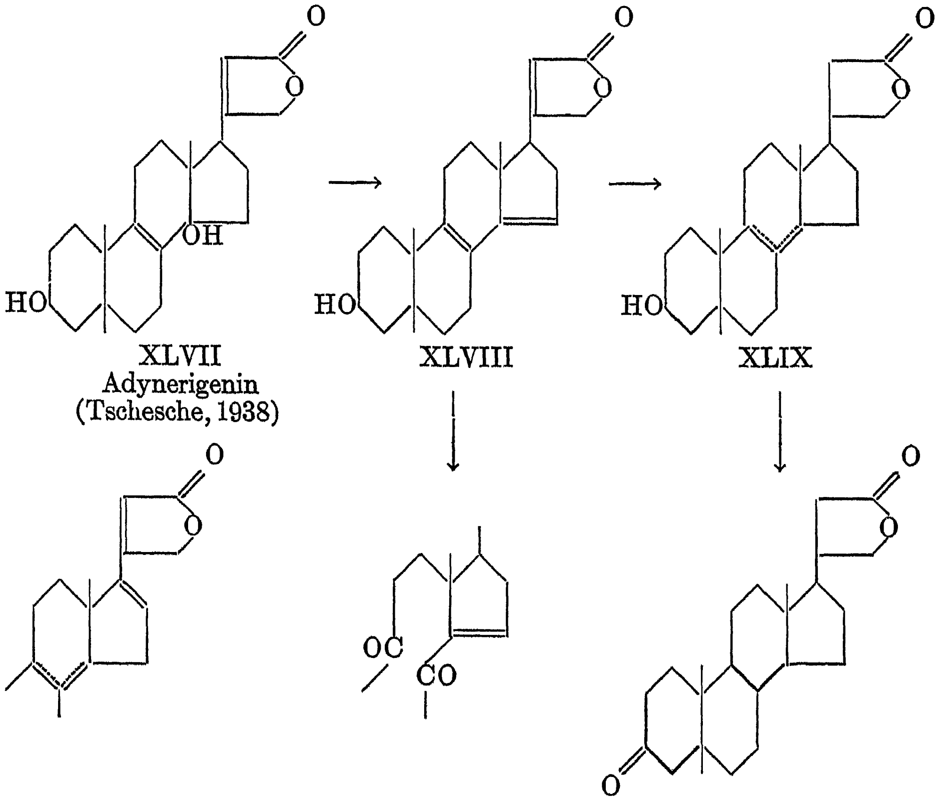
Adynerigenin, according to Tschesche (184, 185), possesses two double bonds, of which only the one associated with the lactone grouping is normally susceptible to catalytic hydrogenation. The second unsaturated linkage, because of its inert character, has been assigned provisonally to the 8,9-position. Of the two hydroxyl groups present in the molecule, one is secondary and attached at C_3; the other is presumably located at the tertiary position C_{14}, since adynerin forms an iso compound in alkaline solution.

Adynerigenin when treated with dilute acid affords an anhydro compound with absorption in the ultraviolet region (247 mμ, log ϵ = 4.1) compatible with structure XLVIII (*cf.* 11, 202). This substance is converted by concentrated hydrochloric acid into an isomeric compound with maximum absorption at 280 mμ (log ϵ = 4.4), which Tschesche described as a derivative containing a conjugated system of double bonds in a single ring. This suggestion is not in accord with the observed spectrum, for a shift of the double bonds to ring D should produce maximum absorption at 330–340 mμ as in the case of dianhydrogitoxigenin (XXIII), whereas compounds like ergosterol and $\Delta^{2,4}$-cholestadiene show much lower extinction (log ϵ = 3.8–4.0) than that exhibited by the rearranged anhydro derivative.

The experimental findings are perhaps better accommodated by a structure

---

[7a] *Added to proof, July 17, 1948:* In a communication that appeared after this manuscript was submitted the conversion of sarmentogenin into methyl 3(β),11(α)-diacetoxyetiocholanate is described (63b). The latter product was identified by comparison with an authentic sample (63a), and the structure of sarmentogenin is thereby established.



XLVII Adynerigenin (Tschesche, 1938)

XLVIII

XLIX

LI

LII

L

of type LI related to monoanhydrogitoxigenin (XXII), for which absorption at 273 mμ (log ε = 4.4) has been reported (85).

In contrast to XLVIII the rearrangement product absorbs 3 moles of hydrogen and gives a mixture from which no crystalline material has been isolated. This result can perhaps be explained by a shift of the isolated double bond from either $C_8:C_9$ or $C_8:C_{14}$ to the conjugated position $C_{14}:C_{15}$ in the presence of the platinum catalyst (*cf.* 160, 192, 200). Hydrogenation of the resulting intermediate might be expected to give a mixture of stereoisomers, as is the case with 20,21-dihydrodianhydrogitoxigenin (199).

Hydrogenation of XLVIII furnishes a tetrahydro derivative XLIX, which can be further reduced by the method of Windaus, Linsert, and Eckhardt (196). Under these conditions the secondary hydroxyl group is lost, but when this group is protected by acetylation a product is obtained after hydrolysis and oxidation that is identical with tetrahydroanhydrodigitoxigenone (L). This evidence establishes C_3 as the location of the secondary hydroxyl group.

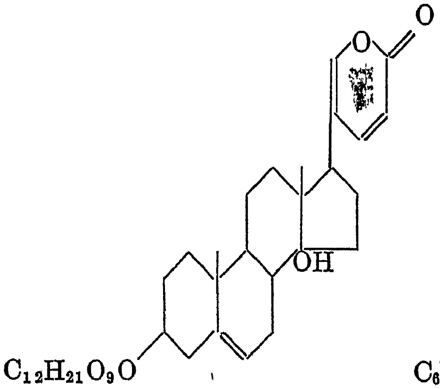
Chromic acid oxidation of XLVIII gives a compound $C_{23}H_{28}O_5$ ($\lambda_{max.}$ = 252 mμ, log ε = 4.1) for which Tschesche proposed formula LII. A neutral product of similar nature, but without characteristic absorption in the ultraviolet, is obtained by oxidation of XLIX.

The glycoside neriantin possesses the formula $C_{29}H_{42}O_9$ and like adynerin contains two double bonds, which, however, are both easily reduced (185). Hydrolysis of the glycoside furnishes glucose and neriantogenin and apparently proceeds without the elimination of a hydroxyl group from the aglycone, since the composition of the latter substance corresponds to the formula $C_{23}H_{32}O_4$. The formation of a diacetyl derivative of the genin indicates the presence of two secondary hydroxyl groups, and treatment with strong acid yields an anhydro compound that has been identified as dianhydrogitoxigenin (XXIII). The diacetate is not identical with 3,16-diacetyl-Δ^{14}-anhydrogitoxigenin from oleandrigenin (94, 180), and in the absence of other evidence the formulation of neriantogenin cannot be made with certainty.

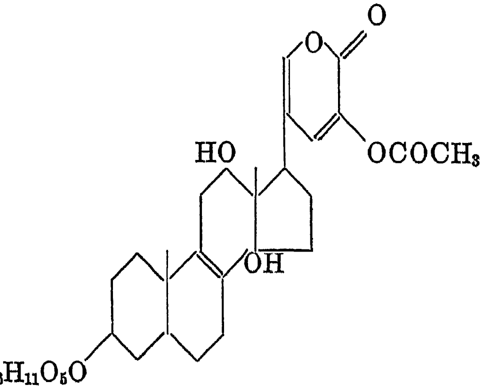
Both neriantin and adynerin are devoid of cardiotonic activity, a fact which suggests the possibility that these substances may be artifacts derived from other glycosides.

D. SCILLAREN A AND SCILLIROSIDE

As a result of the extensive investigations of Stoll and his collaborators (165–171) structures LIII and LIV have been tentatively assigned to scillaren A and to scilliroside. The chemistry of these compounds has been reviewed by Reichstein and Reich (124), Shoppee (151), and Fieser (19b).



LIII
Scillaren A
(Stoll, 1941)

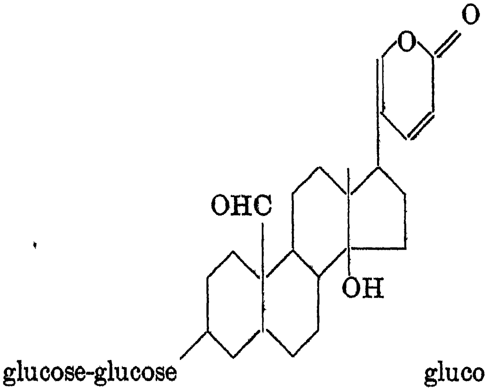


LIV
Scilliroside
(Stoll, 1943)

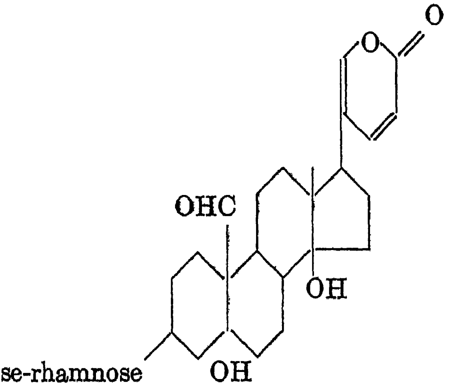
E. HELLEBRIN

For hellebrin, a highly active glycoside obtained from *Helleborus niger* L., W. Karrer has proposed structure LV (62). Like scillaren A and scilliroside, hellebrin shows an absorption band with maximum intensity at 300 mμ (log $\epsilon = 3.8$) characteristic of the α-pyrone side chain. When the glycoside linkage is split by drastic hydrolysis with aqueous or aqueous-alcoholic sulfuric acid, an amorphous product derived from the aglycone is obtained as well as a sugar fraction from which glucose is the only component that can be isolated.

In the course of an investigation of milder conditions of cleavage, it was observed by Schmutz (147) that although Mannich's procedure (78) fails, owing to the extreme insolubility of hellebrin in acetone, a partial hydrolysis takes place in the presence of the enzyme strophanthobiase (59) from the seeds of *S. kombé*. One molecule of glucose is eliminated and a crystalline glycoside desglucohellebrin is formed, which differs from hellebrin in its relatively greater solubility in acetone. On treatment with hydrogen chloride in acetone there are obtained two isomeric substances corresponding to the formula $C_{24}H_{32-34}O_6$ and a reducing sugar identified as rhamnose. The carbohydrate fraction therefore contains one oxygen atom less and the aglycone portion one oxygen atom more than Karrer proposed. These facts are expressed in formula LVI, which has been tentatively advanced by Schmutz.

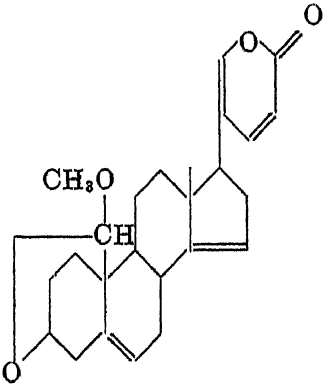


LV
Hellebrin
(W. Karrer, 1943)

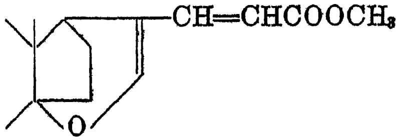


LVI
Hellebrin
(Schmutz, 1947)

The aldehydic character of hellebrin is inferred from the fact that on mild treatment with methanolic hydrogen chloride according to the method of Voss and Vogt (189) a compound $C_{25}H_{30-32}O_4$ is formed, which possesses a methoxyl group but no free hydroxyl groups and no active hydrogen (62). The



LVII



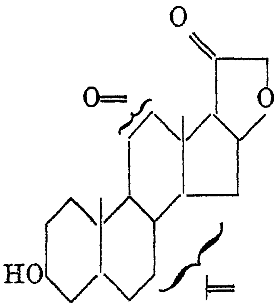
LVIII

ease with which methylation occurs is suggestive of the analogous behavior of strophanthidin (43). The preparation of a crystalline oxime confirms the above view, and the structure of the alcoholysis product is probably correctly represented by LVII.

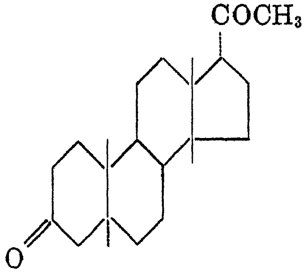
On reaction with hot methanolic potassium hydroxide hellebrin yields isohellebrinic acid methyl ester, for which structure LVIII was suggested by Karrer.

F. DIGININ

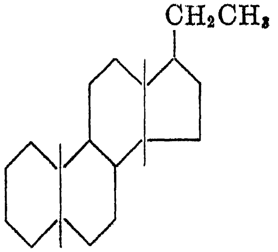
The inactive glycoside diginin, isolated from the leaves of *Digitalis purpurea* by W. Karrer (61), is easily hydrolyzed by the action of dilute mineral acid (154) and yields a sugar, diginose, isomeric with cymarose (155). The aglycone, diginigenin, has the formula $C_{21}H_{28}O_4$ and possesses strong reducing properties. Although the substance gives a positive Legal test with sodium nitroprusside, it does not contain the unsaturated lactone side chain characteristic of other cardiac genins, and on the basis of the following evidence the β-ketotetrahydrofuran structure LIX has been proposed for this compound by Shoppee (153).



LIX
Diginigenin
(Shoppee, 1944)



LX



LXI

Diginigenin is readily converted into a monoacetate and a monosemicarbazone and thus contains a hydroxyl group and a carbonyl group in reactive positions. The presence of a $—COCH_2—$ grouping is indicated by the formation of a piperonylidine derivative. Since diginigenin monoacetate is relatively stable to chromic acid, the presence of other primary or secondary hydroxyl groups is apparently excluded, whereas the absence of tertiary hydroxyl groups is inferred from the stability of the genin to hot aqueous-alcoholic sulfuric acid. Under energetic conditions diginigenin yields a diacetate for which an enol-acetate structure has been suggested.

Evidence for an olefinic linkage is drawn from a positive color reaction with tetranitromethane and from the formation of a tetrahydro derivative from diginigenin on hydrogenation. Tetrahydrodiginigenin gives no response with tetranitromethane, shows no reducing properties, and fails to yield a semicarbazone. Reduction of the reactive carbonyl group therefore accompanies saturation of the double bond. Lack of selective absorption in the ultraviolet excludes the possibility that the double bond is located in a conjugated position.

Although tetrahydrodiginigenin does not form a semicarbazone, an oxime can be obtained under forcing conditions, and on the basis of this and other evidence the presence of a hindered carbonyl group has been postulated.

Neither diginigenin nor its tetrahydro derivative is attacked by periodic acid. Wolff-Kishner reduction of diginigenin followed by hydrogenation affords a mixture from which three products can be isolated (153). One of these substances on oxidation with chromic acid yields 14-iso-17-isoallopregnane-3,20-dione (LX), identified by synthesis from methyl 3(β)-acetoxy-14-iso-17-isoetioallocholanate (CI) (117). Further reduction of LX by the Wolff-Kishner procedure furnishes the hydrocarbon diginane (LXI), which is formulated as 14-iso-17-isoallopregnane (117; *cf.* 89). In view of the possibility of rearrangement in the Wolff-Kishner reaction the orientation assigned to C_{17} in this compound must be regarded as tentative, although certain observations of Meyer (88) would appear to indicate that the 17(α)-configuration is correct.

V. MISCELLANEOUS GLYCOSIDES

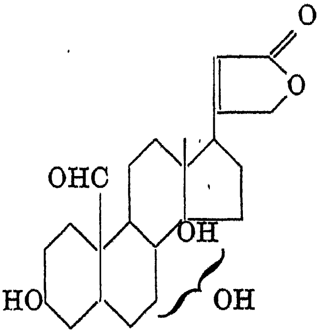
A. NEW GLYCOSIDES

1. *Somalin*

In 1940 Hartmann and Schlittler (30) isolated from the dried roots of *Adenium somalense* Balf. fil. an active principle which they called somalin. The substance was shown by hydrolysis to be a glycoside of cymarose and digitoxigenin.

2. *Adonitoxin*

Two new crystalline compounds have been obtained from *Adonis vernalis* (61, 125, 126). Of these substances one is only slightly active and appears to be an aglycone. The other is the glycoside adonitoxin, melting at 262–265°C. (dec.) and possessing activity intermediate between that of cymarin and convallatoxin. The substance shows maximum absorption at 218 mμ (log ϵ = 4.1), forms an oxime, and yields a carboxylic acid derivative on oxidation with chromic acid.

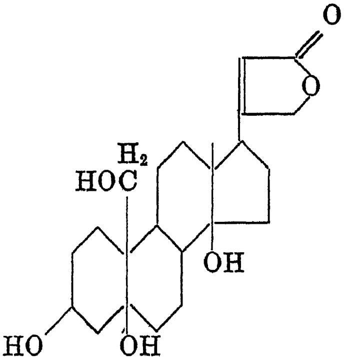


LXII
Adonitoxigenin
(Katz and Reichstein, 1947)

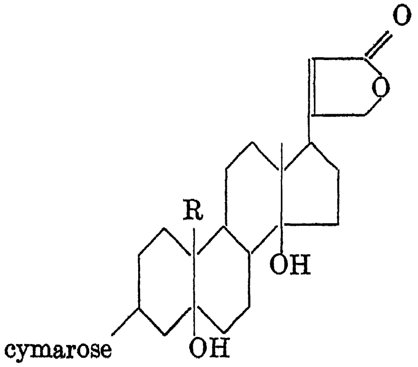
The glycoside linkage when split by hydrogen chloride in acetone yields rhamnose and, in poor yield, adonitoxigenin. The aglycone appears to contain one tertiary and two secondary hydroxyl groups. Formula LXII has been proposed for this genin by Katz and Reichstein (66).

3. Cymarol

A further investigation of the glycosides from *S. kombé* has disclosed the presence of a new substance, cymarol, isolated by chromatographic methods (3). Hydrolysis of the glycoside gives cymarose and a crystalline genin that has been identified as strophanthidol (LXIII), obtained also from strophanthidin by reduction with aluminum isopropoxide (118) or aluminum amalgam (69, 118).



LXIII



LXIV

LXIVa: R = CH_3 Periplocymarin

LXIVb: R = CH_2OH Cymarol

LXIVc: R = CHO Cymarin

LXIVd: R = COOH Cymarylic acid

Cymarol (LXIVb) is intermediate between periplocymarin (LXIVa) and cymarin (LXIVc) with respect to oxygenation at C_{19}, and it was of interest to prepare the fourth member of the series, cymarylic acid (LXIVd), in which carbon atom 19 is present as a carboxyl group. This product is obtained by chromic acid oxidation of cymarin acetate (4), and is considerably less active than the other three glycosides. Convallatoxin acetate has likewise been converted into convallatoxin acid (63), but no data on its physiological activity are available.

4. Convalloside

Related to convallatoxin is a new glycoside, convalloside, isolated from *Convallariae majalis* L. by Schmutz and Reichstein (149). The substance is converted into convallatoxin and glucose by the action of strophanthobiase.

5. *Cheirotoxin*

Schwarz, Katz, and Reichstein (150) have recently obtained a diglycoside of strophanthidin from *Cheiranthus cheiri* L. to which they give the name cheirotoxin. One of the sugar groups is glucose; the other may be a pentose or a methylpentose.

6. *Sarmentoside A and sarmentoside B*

Two substances, sarmentoside A and sarmentoside B, have been isolated from the seeds of *S. sarmentosus* by Schmutz and Reichstein (148). The aglycone obtained from sarmentoside A by cleavage with acetone and hydrogen chloride is probably isomeric with strophanthidin. The sugar component appears to be fucose. In addition to sarmentosigenin A there has been isolated a small amount of a compound, "substance C," that is perhaps an acetone derivative.

Mannich splitting of sarmentoside B gives sarmentosigenin B, which, on the basis of its elementary analysis, is isomeric with strophanthidol (LXIII). The sugar fraction consists of two components, glucose and digitalose.

B. SYNTHETIC GLYCOSIDES FROM NATURAL GENINS

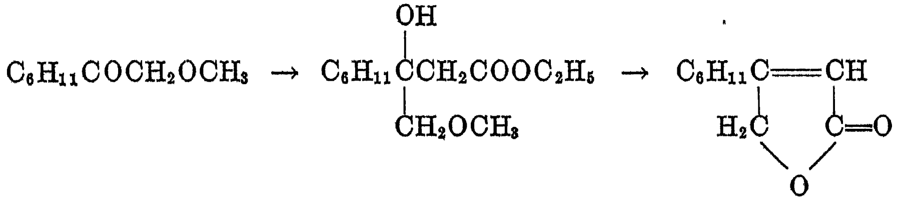
In addition to the synthetic glycosides of strophanthidin (188) that have been tabulated by Reichstein and Reich (124), three new synthetic glycosides derived from other genins have been reported (17). These are digitoxigenin-(3)-β-*d*-glucoside, digoxigenin-(3)-β-*d*-glucoside, and periplogenin-(3)-β-*d*-glucoside. All are prepared by condensation of the aglycones with acetobromoglucose (70), a procedure that is known to give β-glucosides. Attachment of the sugar residue at C_3 is likely, owing to the low reactivity of the hydroxyl groups at C_5, C_{12}, and C_{14}.

The three substances thus obtained are more potent than the natural glycosides digitoxin, digoxin, and periplocymarin (10).[8]

IV. Synthesis of Cardiac Genins

A. LACTONE SIDE CHAIN

In 1940 a method for the preparation of β-substituted α,β-butenolides was reported by Elderfield and his collaborators (23). Methoxymethyl cyclohexyl ketone (LXV), obtained by the reaction of cyclohexylmagnesium bromide and methoxyacetonitrile, is treated with ethyl bromoacetate according to the Refor-



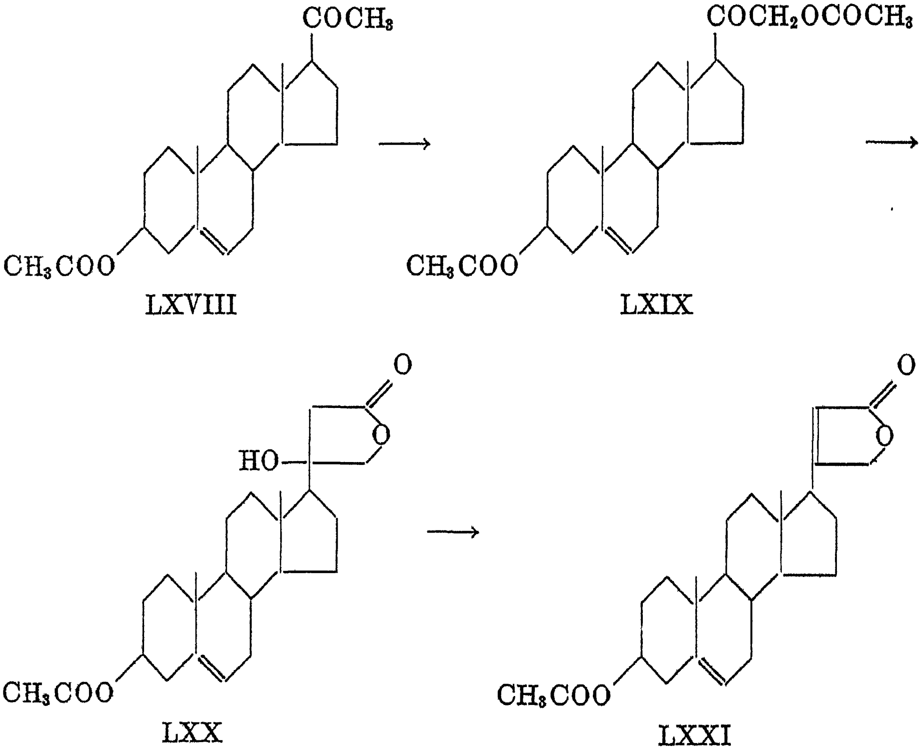
LXV LXVI LXVII

---

[8] Pharmacological data for a number of glycosides and genins are to be found in references 6, 8, 9, 10, and 93.

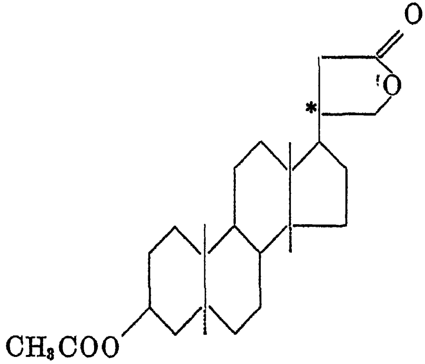
matsky procedure and gives the β-hydroxy ester LXVI. This product when heated with hydrogen bromide undergoes cyclization and dehydration and furnishes the unsaturated lactone LXVII.

Inasmuch as the halides required as starting material for this synthesis are not readily available in the steroid series, the use of acetoxymethyl or benzoxymethyl alkyl ketones rather than the methoxymethyl ketones was investigated (75, 76, 144). These substances are easily obtained from the appropriate etio acids through the acid chlorides and diazoketones (162), or in certain cases from the corresponding methyl ketones with lead tetraacetate (14, 123). Thus 3(β)-acetoxy-Δ^5-pregnen-20-one (LXVIII) with lead tetraacetate yields 3(β), 21-diacetoxy-Δ^5-pregnen-20-one (LXIX) (123), which has been converted into 3(β)-acetoxy-Δ^5-etiocholenylbutenolide (LXXI) by Ruzicka, Reichstein, and Fürst (144). Small amounts of the intermediate hydroxy lactone (LXX) can be isolated from the reaction mixture, but the main product is LXXI.



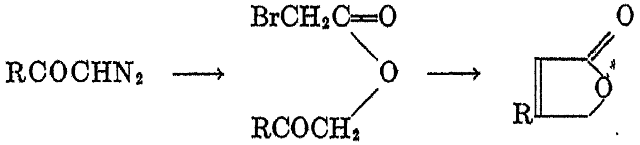
Starting with etiocholanic acid and 3(β)-hydroxyetiocholanic acid, the Columbia investigators (76) prepared the corresponding ketol acetates by the acid chloride-diazoketone route. After treatment with bromoacetic ester and zinc these compounds give, respectively, etiocholanylbutenolide and 3(β)-hydroxyetiocholanylbutenolide. The strong positive nitroprusside (Legal) test and the ultraviolet absorption ($\lambda_{max.} = 217$ mμ, log ϵ = 4.3) exhibited by these lactones are characteristic of the natural cardiac aglycones.

Hydrogenation of LXXI with a platinum catalyst in acetic acid solution gives a mixture from which two isomeric saturated lactones (LXXIIa and LXXIIb) have been isolated (131). Inasmuch as hydrogenation of Δ^5-compounds with few exceptions leads exclusively to compounds of the cholestane series (122, 193), the isomerism must involve the new center of asymmetry at C_{20}. The lactones closely resemble in melting point and specific rotation two saturated lactones obtained by hydrogenation of α-anhydrouzarigenin acetate (174), for which formulas LXXIIa and LXXIIb have also been suggested. These are α_1-tetrahydroanhydrouzarigenin acetate (m.p. 205°C., $[\alpha]_D = +20.2°$) and α_2-tetrahydroanhydrouzarigenin acetate (m.p. 248°C., $[\alpha]_D = +3.9°$), and although a direct comparison between the two series was unfortunately not possible, the identity of the compounds in question is probable. With this reservation the above observations provide evidence for the β-configuration assigned to the C_3-hydroxyl group of uzarigenin (133) (see page 6).



LXXIIa: m.p. 203–204°C., $[\alpha]_D = +19°$
LXXIIb: m.p. 243°C., $[\alpha]_D = +5.9°$

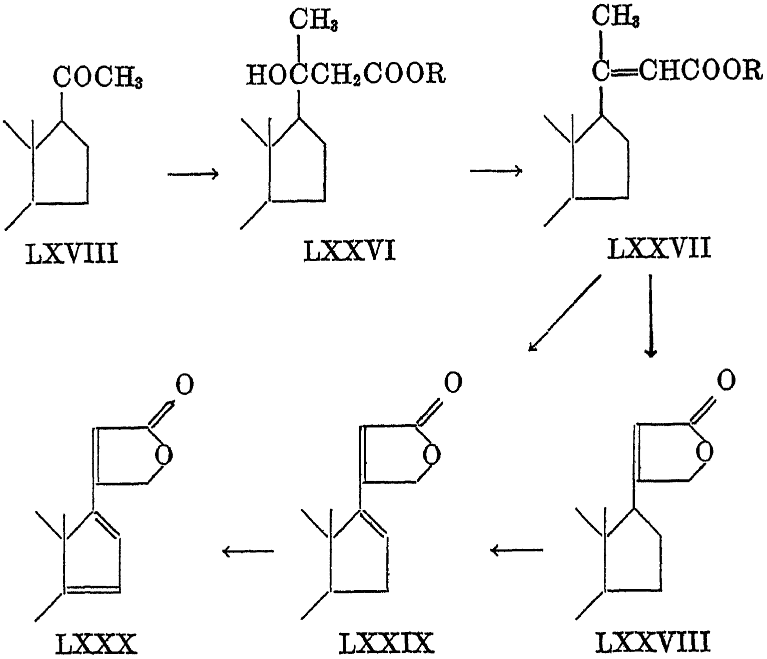
A recent modification of the Reformatsky synthesis was introduced by Plattner and Heusser (99), who treated the intermediate diazoketone LXXIII with bromoacetic acid and obtained the bromoacetate LXXIV. This substance fails to give the unsaturated lactone (LXXV) in the presence of zinc alone, but does so on the addition of ethyl bromoacetate. The mechanism of the conversion of LXXIV into LXXV is therefore not necessarily intramolecular.



LXXIII LXXIV LXXV

The modified procedure gives a somewhat better yield of a more easily purified product than that obtained by the usual method.

Another approach to the preparation of the unsaturated lactone side chain was developed on model compounds by Torrey, Kuck, and Elderfield (173), and was later extended by Ruzicka, Plattner, and Pataki (141) to the preparation of certain unsaturated steroid lactones. 3(β)-Acetoxy-Δ^5-pregnen-20-one (LXVIII) was treated with ethyl bromoacetate and zinc, and the resulting 20-hydroxy norester LXXVI, after saturation of the double bond at C_5:C_6, was dehydrated with acetic anhydride. The product (LXXVII) when heated with selenium dioxide gives 3(β)-acetoxyetioallocholanylbutenolide (LXXVIII) directly, though in rather poor yield. If *N*-bromosuccinimide is used in place of selenium dioxide (143), LXXVIII cannot be isolated, but instead there is obtained in about 10 per cent yield a new product ($\lambda_{max.}$ = 273 mμ, log ε = 4.4) that has been identified as LXXIX by an independent synthesis from 3(β), 21-diacetoxy-Δ^{16}-allopregnen-20-one (101, 137). The reaction of LXXVIII with *N*-bromosuccinimide also furnishes LXXIX (137), which on further treatment with this reagent is converted into the triply unsaturated lactone LXXX (100). The ultraviolet absorption of the latter product ($\lambda_{max.}$ = 333 mμ, log ε = 4.32) corresponds to that of dianhydrogitoxigenin (XXIII) (180).

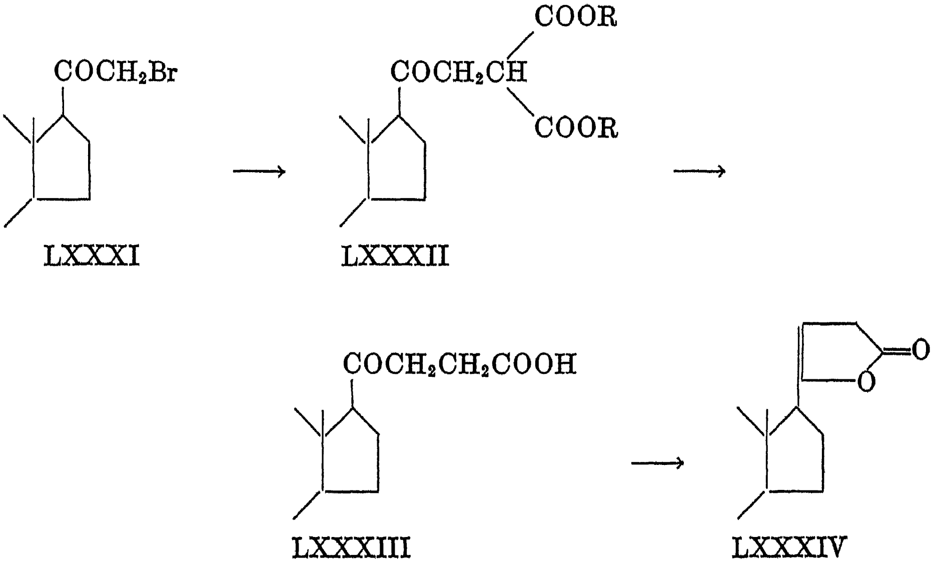


By application of the methods described above α,β-butenolides substituted in the β-position by the following groups have been prepared: cyclohexyl (75), 4-hydroxycyclohexyl (28, 29), 3,4-dihydroxycyclohexyl (27), phenyl (75, 173), *p*-hydroxyphenyl (82), *m*-hydroxyphenyl (82), decahydro-β-naphthyl (68), 6-hydroxy-2-naphthyl (68), 1-hydrindanyl (68), etiocholanyl (76), 3(α)-hydroxyetiocholanyl (130), 3(β)-hydroxyetiocholanyl (76), 3(α),12(α)-dihydroxyetiocholanyl (142), 3(α),7(α),12(α)-trihydroxyetiocholanyl (34), etioallocholanyl (106), Δ^2-etioallocholenyl (97), 3(α)-hydroxyetioallocholanyl (106), 3(β)-hydroxyetioallocholanyl (106, 132, 137), 3(β)-hydroxy-Δ^{16}-etioallocholenyl

(137, 143), 2,3-dihydroxyetioallocholanyl (97), 3(β),5-dihydroxyetioallocholanyl (138), 3(β)-hydroxy-Δ^5-etiocholenyl (99, 131, 144), 3(β)-hydroxyetioallocholanylmethyl (98), 3(β)-hydroxy-Δ^5-etioallocholenylmethyl (98), norcholanyl (67), 3(β)-hydroxy-Δ^5-norcholenyl (99, 134), and 3(α),7(α),12(α)-trihydroxynorcholanyl (67, 135). Allouzarigenin has also been prepared (109).

Two derivatives that are further substituted by a methyl group in the α-position of the lactone ring have been synthesized (136). These are β'-(3(β)-hydroxy-Δ^5-etiocholenyl-17)-α'-methyl-$\Delta^{\alpha',\beta'}$-butenolide and β'-(3(β)-hydroxy-Δ^5-norcholenyl-23)-α'-methyl-$\Delta^{\alpha',\beta'}$-butenolide.

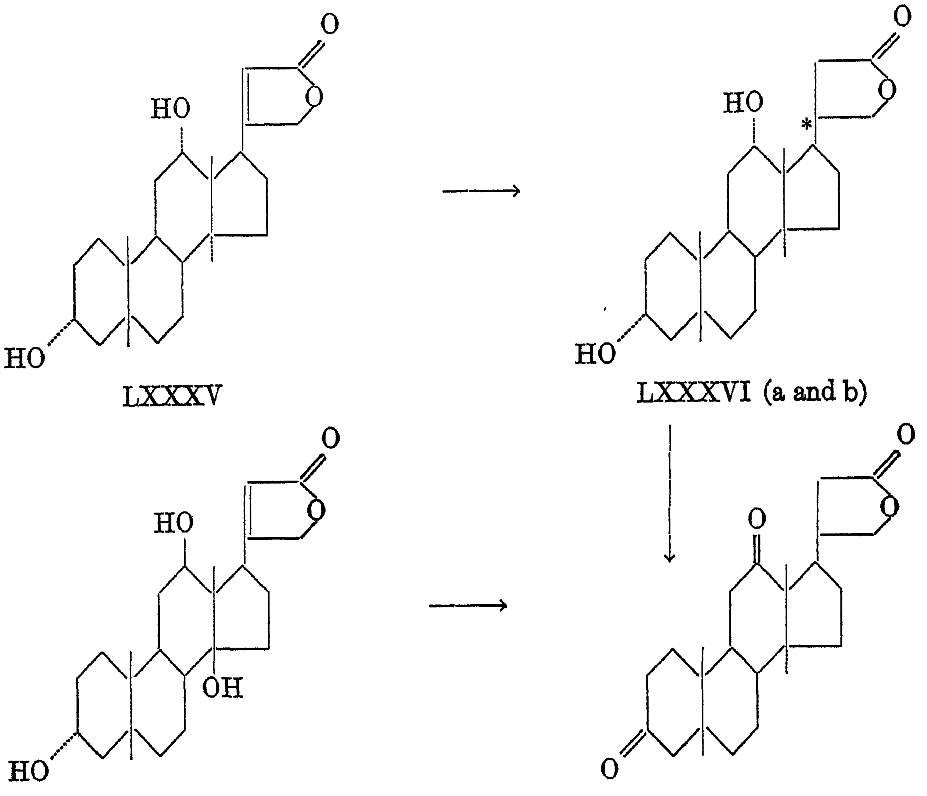
The synthesis of two γ-substituted β,γ-butenolides has also been carried out (102) for which purpose 3(β)-hydroxy-21-bromo-Δ^5-pregnen-20-one (LXXXI) serves as the starting material. Treatment of this substance with sodiomalonic ester gives LXXXII, which on decarboxylation is converted into the γ-keto acid LXXXIII. The latter compound yields the β,γ-unsaturated lactone LXXXIV with acetic anhydride and acetyl chloride. Hydrogenation of the 5,6-double bond of LXXXIII prior to lactonization affords the corresponding γ'-(3(β)-hydroxyetioallocholanyl)-β',γ'-butenolide. The ultraviolet absorption spectra of both products are consistent with the proposed structures.



LXXXI LXXXII LXXXIII LXXXIV

Two of the synthetic lactones listed above, 3(β)-hydroxy-Δ^5-etiocholenylbutenolide and 3(β)-hydroxy-Δ^5-norcholenylbutenolide, have been converted into the corresponding glucosides (91, 115). The maltoside of the former has likewise been prepared (91).

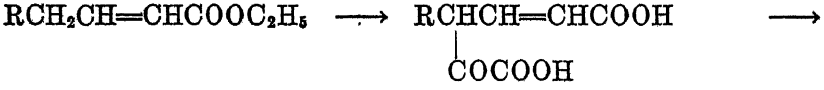
The following reactions have been carried out with etiodesoxycholylbutenolide (LXXXV) and provide additional correlation of the synthetic lactones with those of natural origin (113). Hydrogenation of LXXXV gives a mixture from which two epimeric saturated lactones (LXXXVIa and LXXXVIb) have been


LXXXV LXXXVI (a and b)

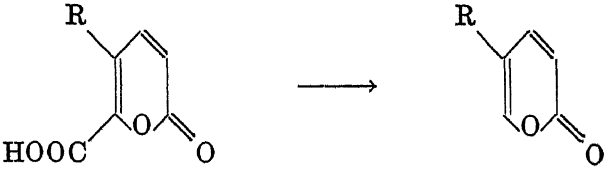
II LXXXVII

isolated. One of these on oxidation yields a diketone identical with tetrahydroanhydrodigoxigenone (LXXXVII) from digoxigenin (II) (181).

The synthesis of certain 5-substituted α-pyrones analogous to the side-chain structures of scillaren A and hellebrin has been investigated by Fried and Elderfield (22; *cf.* 23). The alkyl crotonic ester (LXXXVIII) is condensed with ethyl oxalate, and after hydrolysis the ketodicarboxylic acid (LXXXIX) is obtained. Cyclization of LXXXIX takes place under the influence of hydrogen bromide in acetic acid, and the resulting 5-alkyl-6-carboxy-α-pyrone (XC) affords the 5-alkyl-α-pyrone (XCI) on decarboxylation with copper powder.


$$\mathrm{RCH_2CH{=}CHCOOC_2H_5} \longrightarrow \mathrm{R}\underset{\displaystyle\mathrm{COCOOH}}{\underset{|}{\mathrm{C}}}\mathrm{HCH{=}CHCOOH} \longrightarrow$$

LXXXVIII LXXXIX

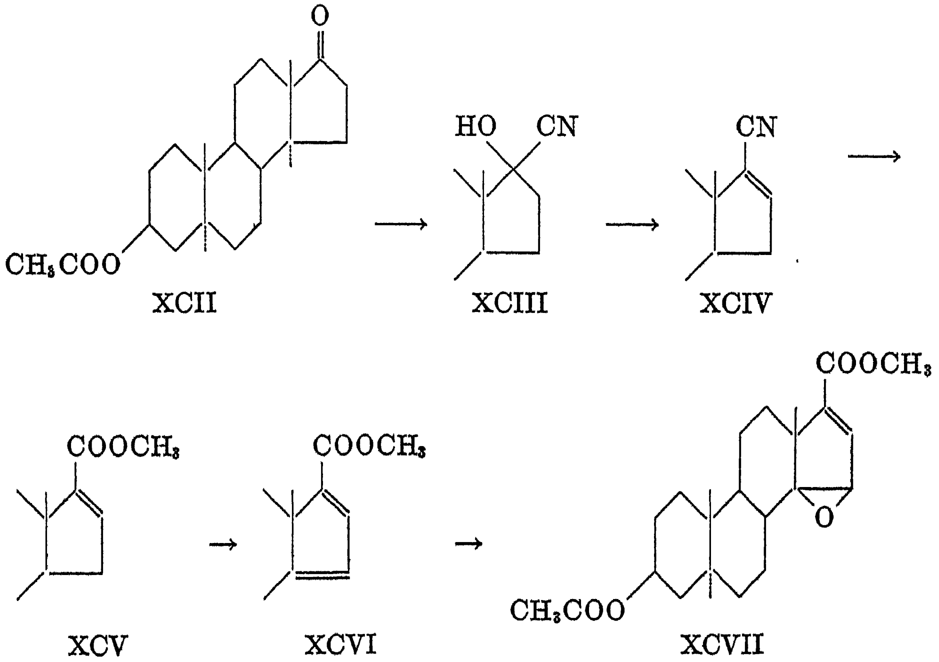

XC XCI

The synthesis is successful when R is a methyl or ethyl group, and the absorption spectra of these products ($\lambda_{max.}$ = 300 mμ, log ε = 3.7) closely resemble those of scillaren A and hellebrin. The method fails, however, when R is a cyclohexyl group. Attempts to effect suitable conversions from α-pyrone-5-carboxylic acid have likewise been unsuccessful.

B. C_{14}-HYDROXYL GROUP

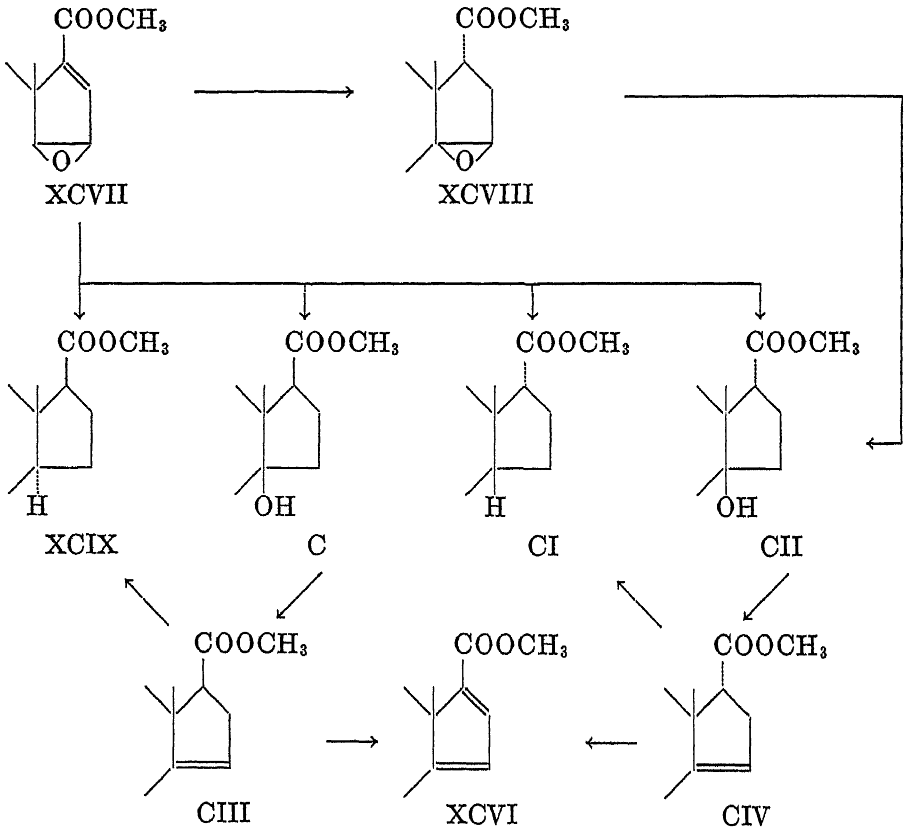
For the introduction of a hydroxyl group at C_{14}, compounds possessing a conjugated system extending to this point (*cf.* LXXX) have been employed by Ruzicka *et al.* (111, 140). Preliminary experiments were carried out with methyl 3(β)-acetoxy-$\Delta^{14,16}$-etioallocholadienate (XCVI), which is readily available from 3(β)-acetoxyandrostan-17-one (190) by the transformations XCII → XCVI. The last step in this series is accomplished with *N*-bromosuccinimide and furnishes the doubly unsaturated ester XCVI ($\lambda_{max.}$=292 mμ, log ε = 4.2) in 77 per cent yield.

XCVI reacts with only 1 mole of perbenzoic acid and gives an oxide to which the 14,15-epoxy structure XCVII is assigned on the basis of an absorption maximum at 233 mμ, log ε = 3.86 (*cf.* 172). Hydrogenation of this product in the presence of palladium yields a saturated epoxy ester (XCVIII), but when platinum is used as the catalyst, rupture of the oxide ring takes place in addition to reduction of the olefinic linkage. From the hydrogenation mixture four products, XCIX, C, CI, and CII, have been separated by chromatographic methods. Two of these products, C and CII, contain hydroxyl groups that are resistant to acetylation and to oxidation with chromic acid and must therefore be located at



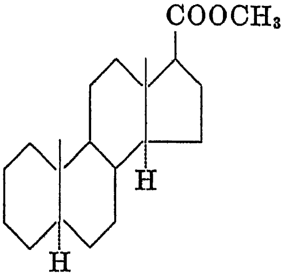
the tertiary position C_{14}. The two remaining products, XCIX and CI, were shown by analysis to have suffered the loss of an oxygen atom, and of these XCIX was identified as methyl 3(β)-acetoxyetioallocholanate.

In order to establish the configurations of the hydroxy esters C and CII, the centers of asymmetry at C_{14} were first eliminated by dehydration with phosphorus oxychloride and pyridine. The unsaturated esters CIII and CIV formed in this way are isomers, and since both are easily reduced it is assumed that in each the unsaturated linkage occupies the 14,15-position. The isomerism must therefore involve the configuration at C_{17}, a view that is confirmed by the conversion of both substances into XCVI, in which asymmetry at this point is absent. Inasmuch as hydrogenation of CIII gives XCIX, for which the β-arrangement at C_{17} is established, assignment of the β-configuration to CIII and C and the α-configuration to CIV and CII as well as to CI, the reduction product of CIV, is undoubtedly correct.

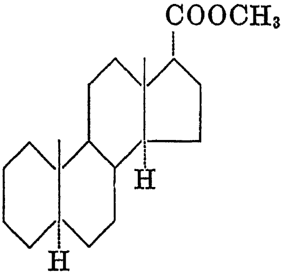


CI, however, differs from the known methyl 3(β)-acetoxy-17-isoetioallocholanate (157), and replacement of the oxygen at C_3 by hydrogen affords an ester (CVII) that is not identical with methyl 17-isoetioallocholanate (CVI) (18). It is therefore concluded that the non-identity of the compounds in question is the result of a difference in spatial arrangement at C_{14}, and that CI has a *cis* C/D ring fusion.[9]

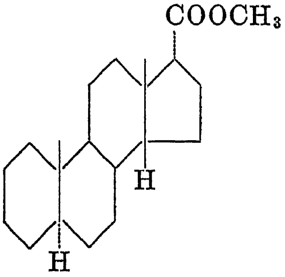
Evidence that may support the above formulation has been drawn from a study of the rates of hydrolysis of the three known methyl etioallocholanates CV (176, 177), CVI (18), and CVII (112), of which the latter is derived from CI. From an inspection of molecular models, it can be predicted (33) that, in terms of hindrance of the ester groups, the 14-iso-17-iso compound (CVII) should resemble methyl etioallocholanate (CV), which is less hindered than methyl 17-isoetioallocholanate (CVI). This prediction has been tested experimentally by measurements of the per cent of ester hydrolyzed in 1 hr. under standardized conditions. The results obtained with the three esters are as follows: CV, 48.3 per cent and 44.1 per cent; CVI, 17.8 per cent; CVII, 48.6 per cent. The fourth member of the series, methyl 14-isoetioallocholanate, is unknown but should be comparable to CV and CVII rather than to CVI.



CV



CVI



CVII

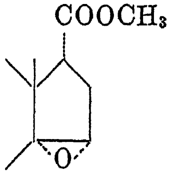
With regard to the configurations of the tertiary hydroxyl groups in C and CII, it can be assumed that these groups are similarly oriented since both are derived from the same oxide (XCVII). In each case dehydration can be accomplished with phosphorus oxychloride in pyridine, but whereas this reaction occurs quantitatively at room temperature with CII, higher temperatures are required for the elimination of water from C (110). It is apparent from a study of models of the four possible hydroxy esters epimeric at C_{14} and C_{17} that hindrance of the hydroxyl group is considerably greater in the two products in which this group is *cis* to the side chain at C_{17} than in the corresponding *trans* compounds. It follows from this argument that the arrangement of the substituents at C_{14} and C_{17} is *trans* in CII and *cis* in C. Since for the latter compound the β-orientation of the side chain has been established by the conversion of C into XCIX, the β-configuration must likewise be assigned to the hydroxyl group at C_{14}. This evidence also implies the β-configuration for the tertiary hydroxyl group in CII.

Although no lactone has been obtained from the free acid of C, such a lactonization would appear to be excluded by the blocking effect of the angular methyl group at C_{13}. A similar phenomenon has been observed by Sorkin and Reichstein (158) in the case of 12-epietiodesoxycholic acid (III).

---

[9] The influence of the configuration at C_{17} on the steric course of hydrogenation of the 14,15-double bond has also been observed by Speiser and Reichstein (159) and by Meyer (85, 87). It is of interest in this connection that hydrogenation of XCVI yields both XCIX and CI, but not the corresponding 14-normal-17-iso or 14-iso-17-normal compounds, a result that suggests a 1,4-*cis* addition of hydrogen at C_{14} and C_{17} (*cf.* 74).

Inasmuch as hydrogenation of other steroid oxides gives rise to hydroxy compounds of the same stereochemical series as the oxides from which they are derived (25, 77, 95, 103, 116), the oxide bridge of XCVII is undoubtedly β-oriented. The formation of α-oxides, however, has been observed in the reaction of peracids with Δ^{14}-monounsaturated esters. CIV, for example, gives a product CVIII that differs from XCVIII and that is not subject to hydrogenolysis with platinum in either alcohol or acetic acid (110).



CVIII

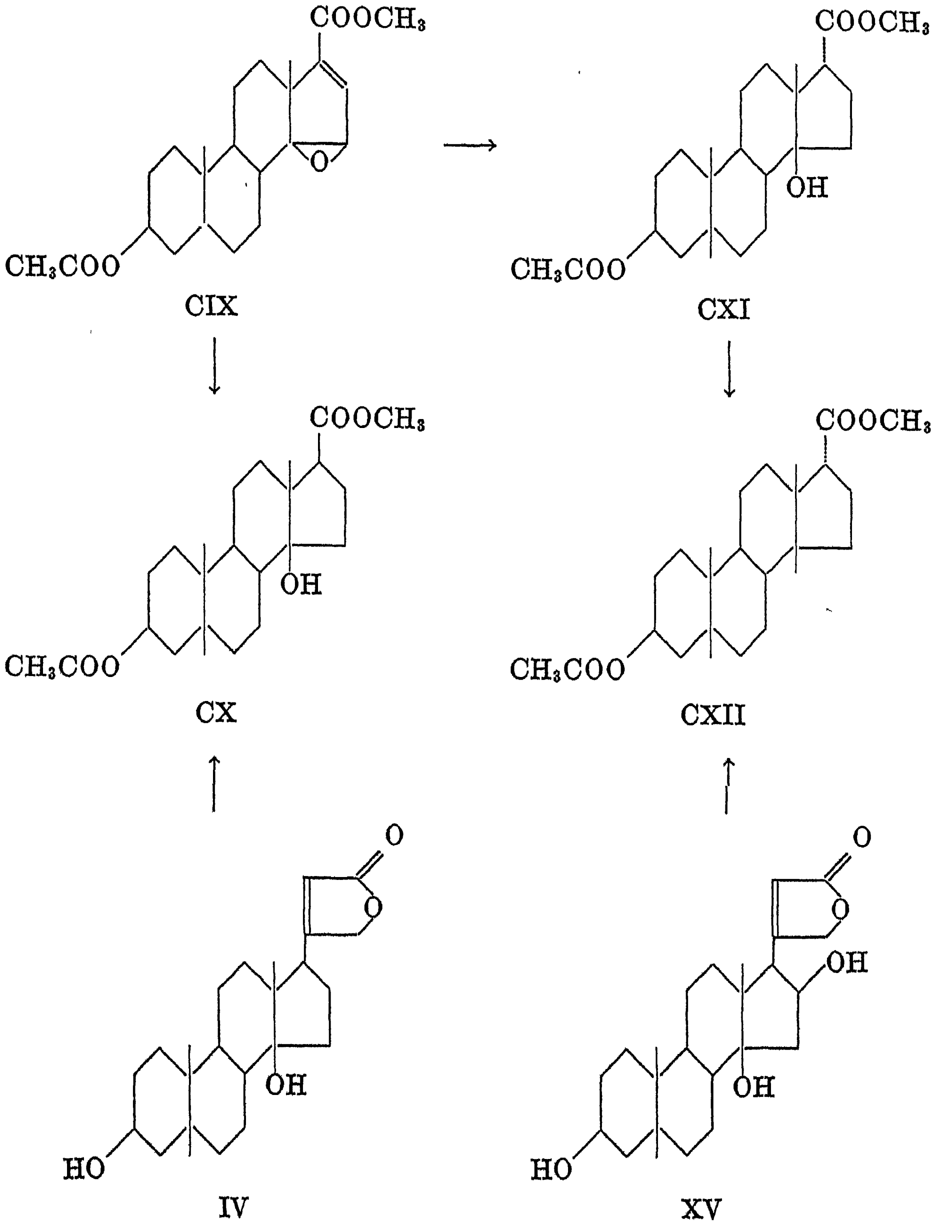
It was shown in an earlier section (page 4) that the C_{14}-hydroxyl group of the natural cardiac aglycones has the β-configuration. By hydrogenation of methyl 3(β)-acetoxy-14(β),15(β)-epoxy-Δ^{16}-etiocholanate (CIX) Ruzicka and his associates (139) have for the first time obtained by synthetic means an aglycone derivative possessing an intact hydroxyl group at C_{14}. From the mixture of products obtained by hydrogenation of CIX, two hydroxy esters (CX and CXI) have been isolated whose structures are analogous to those of C and CII. Of these, CX is identical with a degradation product of digitoxigenin (IV) (36). The other product (CXI) on dehydration and hydrogenation gives the ester CXII, that differs from methyl 3(β)-acetoxyetiocholanate (120) and methyl 3(β)-acetoxy-17-isoetiocholanate (157), but is identical with the reduction product of dianhydrogitoxigenin acetate from gitoxigenin (XV).

The methods described above for the introduction of a hydroxyl group at C_{14} have been extended to the preparation of certain 14-hydroxy-20-keto derivatives for which the unsaturated ketone CXIII serves as starting material (107). This substance is obtained by the conversion of 3(β)-acetoxyallopregnan-20-one into 3(β)-acetoxy-Δ^{16}-allopregnen-20-one (80), followed by treatment of the latter compound with *N*-bromosuccinimide (107). A better method consists in the reaction of the unsaturated nitrile XCIV with *N*-bromosuccinimide and conversion of the doubly unsaturated product into CXIII by the action of methylmagnesium bromide (104).

CXIII with monoperphthalic acid furnishes the oxide CXIV, which, after hydrogenation with a palladium catalyst and regeneration of the C_{20}-keto group by chromic acid oxidation, gives the hydroxy ketone CXV in about 50 per cent yield. Small amounts of an isomer (CXVIII) and of the two desoxy compounds CXVI and CXVII[10] are also obtained.

---

[10] This substance is the main product when the hydrogenation of CXIV is carried out with platinum instead of palladium.



CIX

CXI

CX

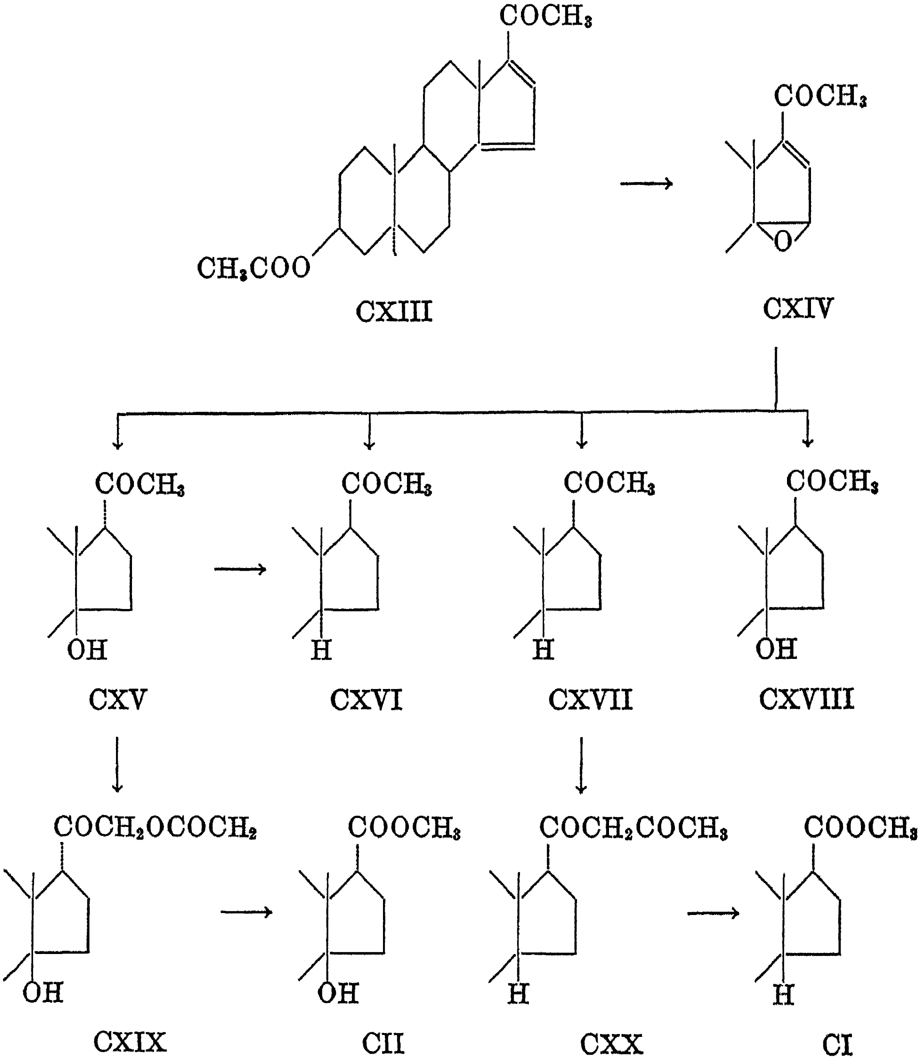
CXII

IV
Digitoxigenin

XV
Gitoxigenin

The structures assigned to CXV and CXVII are based on the reactions of these compounds with lead tetraacetate to give the ketol acetates CXIX and CXX, which yield methyl 3(β)-acetoxy-14(β)-hydroxy-17-isoetioallocholanate (CII) and methyl 3(β)-acetoxy-14-iso-17-isoetioallocholanate (CI), respectively, on further oxidation with periodic acid (107, 108).

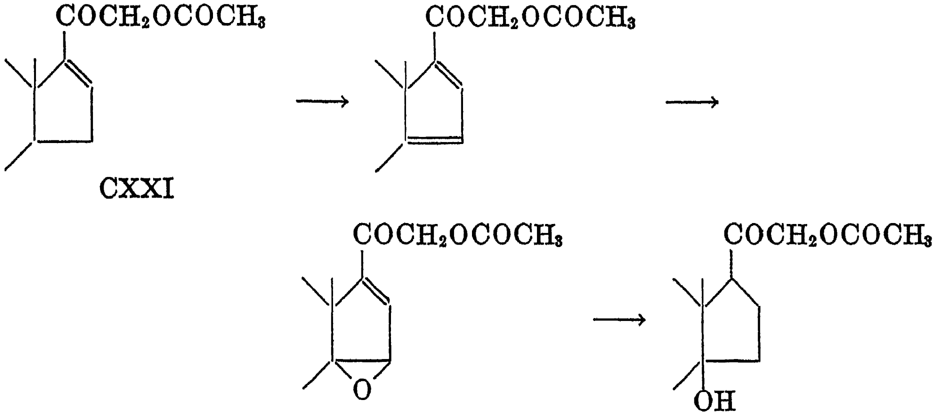
Although dehydration and hydrogenation of CXV give 3(β)-acetoxyallopregnan-20-one (CXVI) in which the β-configuration at C_{17} is known, it is unlikely that CXV can have a β-arrangement at this point, in view of its conversion under



mild conditions into the 17(α)-ester CII. The 17(α)-orientation of CXV is further supported by evidence drawn from a comparison of specific rotations, and it must therefore be assumed that a rearrangement of the side chain of CXV occurs during the dehydration.

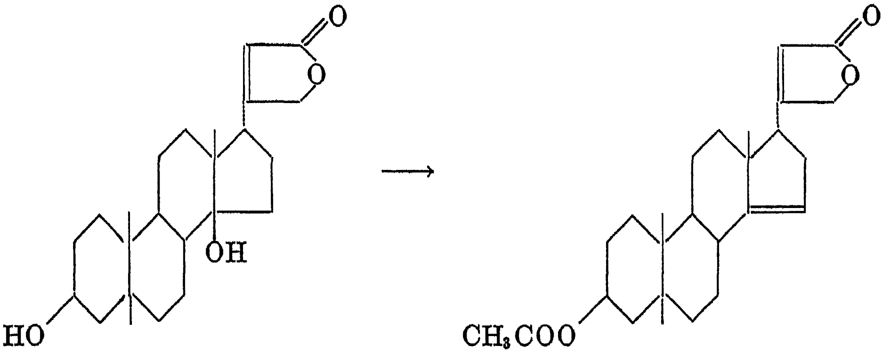
Only very small amounts of CXVIII are obtained by the procedure described above, and its formulation is based on analogy to the earlier work (110).

The ketol acetate CXIX, which has also been obtained by the transformations CXXI → CXIX (108), possesses the grouping at C_{17} required for elaboration of



CXXI CXIX

an unsaturated lactone side chain. Treatment of this substance with bromoacetic ester in the presence of zinc affords the lactone CXXII in a yield of about 17 per cent (109). The product possesses all the structural features that have been attributed to the aglycone uzarigenin, with the exception of the α-orientated side chain at C_{17}. In this respect CXXII resembles allostrophanthidin and alloperiplogenin, and it is therefore called allouzarigenin. Since uzarigenin itself is not known, the synthetic lactone (CXXII) was dehydrated for comparison with material of natural origin. The anhydro derivative (CXXIII), as expected, differs from both the α- and β-anhydrouzarigenins of Tschesche (174). The difference in specific rotation between CXXII and CXXIII is similar to that observed between the allogenins and their anhydro derivatives and is considerably greater than the corresponding rotational differences in the normal series.

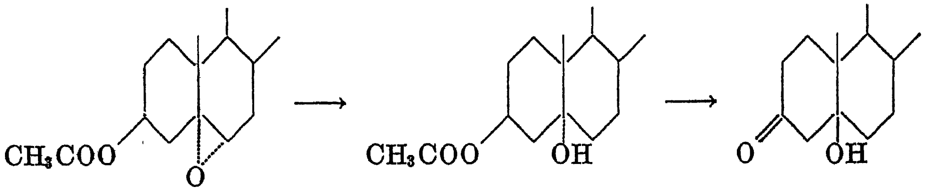


CXXII CXXIII

c. C_5-HYDROXYL GROUP

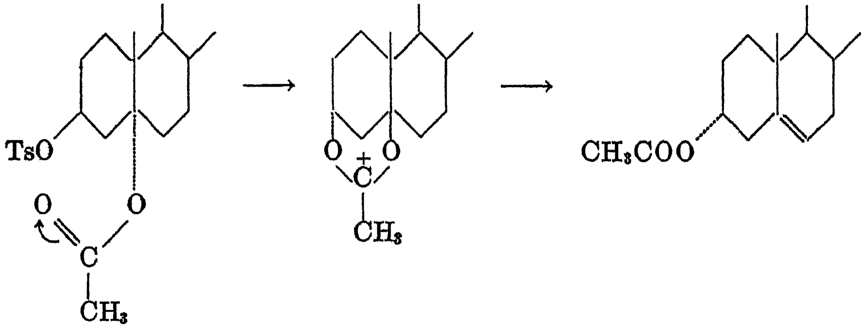
In strophanthidin, periplogenin and other related aglycones the presence of a 5(β)-hydroxyl group has been established (page 9). The hydrogenation of 4,5- and 5,6-oxides has been explored as a route to compounds of this type.

Reduction of α-cholesterol oxide acetate (CXXIV)[11] with platinum in acetic acid proceeds with the absorption of 1 mole of hydrogen and gives in good yield a compound (CXXV) that contains a free hydroxyl group (105). In the presence of chromic acid CXXV forms a golden yellow chromate ester but is otherwise unattacked, whereas saponification and oxidation of CXXV gives the hydroxy ketone CXXVI, which is easily converted into Δ^4-cholesten-3-one by loss of water. This evidence establishes C_5 as the location of the new hydroxyl group, and since a rupture of the bond from C_5 to oxygen is not involved in the formation of CXXV from CXXIV, the α-configuration is assigned to the C_5-hydroxyl group. This arrangement is opposite to that found in the natural cardiac genins.



CXXIV CXXV CXXVI

Under energetic conditions (dimethylaniline–acetyl chloride) CXXV yields a 3,5-diacetate, which gives 3(β)-hydroxy-5-acetoxycholestane on partial saponification. The transformation of the latter compound into epicholesteryl acetate (CXXVIII) on heating with p-toluenesulfonyl chloride and pyridine provides additional evidence for the α-orientation of the hydroxyl group at C_5, in view of the steric requirements of the intermediate CXXVII.[12]



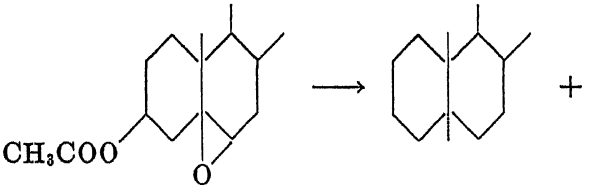
CXXVII CXXVIII

The hydrogenation of β-cholesterol oxide acetate (CXXIX)[11] takes place with the absorption of somewhat more than 1 mole of hydrogen and follows a different course from that observed for the α-oxide (CXXIV). A mixture of products is obtained from which cholestane (CXXX), cholestanyl acetate (CXXXI), and 3(β)-acetoxy-6(β)-hydroxycholestane (CXXXII) have been isolated. The latter substance was converted into the known compounds 3(β),6(β)-diacetoxycholestane (81) and 6-ketocholestanyl acetate (194). The inversion of configuration at C_5 that accompanies the hydrogenation can perhaps be attributed to adsorption of the α-face of CXXIX on the catalyst surface (*cf.* 74).

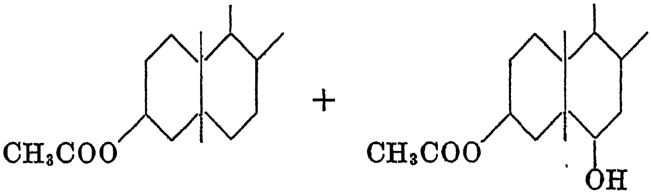
---

[11] The trivial indices α and β were applied to the two oxides of cholesterol by Westphalen (191). It was subsequently shown that the so-called "β-oxide" is a molecular compound of a true β-oxide and the α-isomer (1, 31). The correctness of the designations α and β as applied to the true oxides has been established by Plattner and Lang (103). Of interest in this connection is the conversion of β-cholesterol oxide into the α-isomer by Fürst and Koller (24).

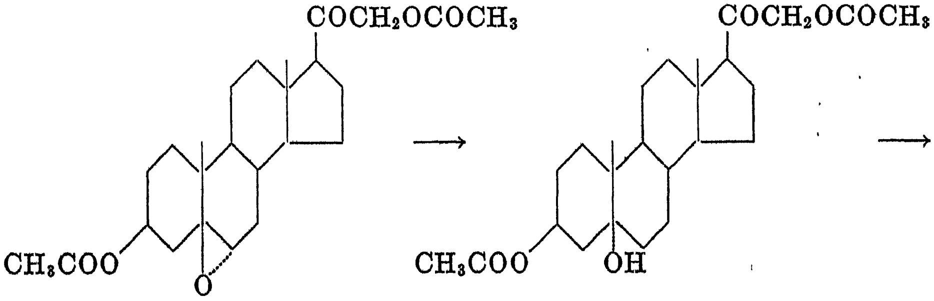
[12] The mechanism suggested for this reaction is based on the work of Winstein, Hess, and Buckles (201).



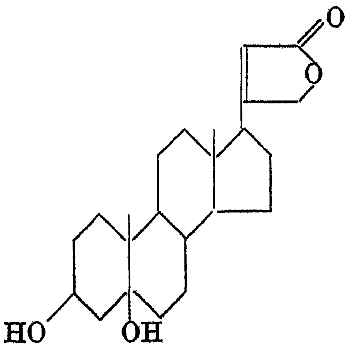
CXXIX CXXX



CXXXI CXXXII



CXXXIII CXXXIV



CXXXV

Results similar to those described for the cholesterol oxides have been observed by Ruzicka and Muhr (129) in the reduction of the α- and β-oxides of dehydroisoandrosterone acetate. In addition, the reduction of two oxides of uncertain configuration has been investigated by Plattner, Petrzilka, and Lang (105). These compounds are 5,6-epoxycholestane, m.p. 80°C. (127), and 4,5-epoxycholestane, m.p. 96°C. (32). In both instances hydrogenation leads to a mixture of products from which a 5-hydroxy derivative has been isolated. The configuration of the hydroxyl group in this compound is unknown.

By the hydrogenation of 3(β),21-diacetoxy-5,6-epoxyallopregnan-20-one (CXXXIII) a 5(α)-hydroxy compound (CXXXIV) is obtained that on treatment with zinc and bromoacetic ester yields a lactone (CXXXV) with maximum absorption at 219 mμ, log ϵ = 4.3 (138). This substance differs from periplogenin in the absence of a hydroxyl group at C_{14} and in the configuration at C_5.

VII. REFERENCES

(1) BAXTER AND SPRING: J. Chem. Soc. **1943**, 613.
(2) BLOCH AND ELDERFIELD: J. Org. Chem. **4**, 289 (1939).
(3) BLOME, KATZ, AND REICHSTEIN: Pharm. Acta Helv. **21**, 325 (1946).
(4) BLOME AND REICHSTEIN: Pharm. Acta Helv. **22**, 235 (1947).
(5) BUTENANDT AND GALLAGHER: Ber. **72**, 1866 (1939).
(5a) BUZAS AND REICHSTEIN: Helv. Chim. Acta **31**, 84 (1948).
(6) CHEN: Ann. Rev. Physiol. **7**, 681 (1945).
(7) CHEN AND CHEN: J. Pharmacol. Exptl. Therap. **49**, 561 (1933); **51**, 23 (1934); J. Biol. Chem. **105**, 231 (1934).
(8) CHEN, CHEN, AND ANDERSON: J. Am. Pharm. Assoc. **25**, 579 (1936).
(9) CHEN AND ELDERFIELD: J. Pharmacol. Exptl. Therap. **76**, 81 (1942).
(10) CHEN, ELDERFIELD, UHLE, AND FRIED: J. Pharmacol. Exptl. Therap. **77**, 401 (1943).
(11) DANNENBERG: *Über die Ultraviolettabsorption der Steroide.* Verlag der Akademie der Wissenschaften, Berlin (1940).
(12) EHRENSTEIN: J. Org. Chem. **9**, 435 (1944).
(13) EHRENSTEIN AND JOHNSON: J. Org. Chem. **11**, 823 (1946).
(14) EHRHARDT, RUSCHIG, AND AUMÜLLER: Z. angew. Chem. **52**, 363 (1939); Ber. **72**, 2035 (1939).
(15) ELDERFIELD: Chem. Revs. **17**, 187 (1935).
(16) ELDERFIELD: J. Biol. Chem. **113**, 631 (1936).
(17) ELDERFIELD, UHLE, AND FRIED: J. Am. Chem. Soc. **69**, 2235 (1947).
(18) VON EUW AND REICHSTEIN: Helv. Chim. Acta **27**, 1851 (1944).
(19) FIESER: *Chemistry of Natural Products Related to Phenanthrene*, 2nd edition, Reinhold Publishing Corporation, New York (1937): (a) p. 285; (b) p. 295; (c) p. 398.
(20) FIESER AND JACOBSEN: J. Am. Chem. Soc. **59**, 2335 (1937).
(21) FIESER AND NEWMAN: J. Biol. Chem. **114**, 705 (1936).
(22) FRIED AND ELDERFIELD: J. Org. Chem. **6**, 566, 577 (1941).
(23) FRIED, RUBIN, PAIST, AND ELDERFIELD: Science **91**, 435 (1940).
RUBIN, PAIST, AND ELDERFIELD: J. Org. Chem. **6**, 260 (1941).
Cf. RANGANATHAN: Current Sci. **9**, 458 (1940).
(24) FÜRST AND KOLLER: Helv. Chim. Acta **30**, 1454 (1947).
(25) GALLAGHER AND LONG: J. Biol. Chem. **162**, 495 (1946).
(26) GALLAGHER AND LONG: J. Biol. Chem. **162**, 521 (1946).
(27) HARDEGGER: Helv. Chim. Acta **29**, 1195 (1946).
(28) HARDEGGER, HEUSSER, AND BLANK: Helv. Chim. Acta **29**, 477 (1946).

(29) Hardegger, Plattner, and Blank: Helv. Chim. Acta **27**, 793 (1944).
(30) Hartmann and Schlittler: Helv. Chim. Acta **23**, 548 (1940).
(31) Hattori: J. Pharm. Soc. Japan **60**, 334 (1940); Chem. Abstracts **34**, 7294 (1940).
(32) Heilbron, Shaw, and Spring: Rec. trav. chim. **57**, 529 (1938).
(33) Heusser, Meier, and Ruzicka: Helv. Chim. Acta **29**, 1250 (1946).
(34) Heusser and Wuthier: Helv. Chim. Acta **30**, 1460 (1947).
(35) Huebner, Lohmar, Dimler, Moore, and Link: J. Biol. Chem. **159**, 503 (1945).
(36) Hunziker and Reichstein: Experientia **1**, 90 (1945); Helv. Chim. Acta **28**, 1472 (1945).
(37) Jacobs: J. Biol. Chem. **57**, 553 (1923).
(38) Jacobs: J. Biol. Chem. **88**, 519 (1930).
(39) Jacobs: Physiol. Revs. **13**, 222 (1933).
(40) Jacobs and Bigelow: J. Biol. Chem. **96**, 647 (1932).
(41) Jacobs and Bigelow: J. Biol. Chem. **99**, 521 (1933).
(42) Jacobs and Bigelow: J. Biol. Chem. **101**, 15 (1933).
(43) Jacobs and Collins: J. Biol. Chem. **59**, 713 (1924).
(44) Jacobs and Collins: J. Biol. Chem. **61**, 387 (1924).
(45) Jacobs and Collins: J. Biol. Chem. **65**, 491 (1925).
(46) Jacobs and Elderfield: J. Biol. Chem. **92**, 313 (1931).
(47) Jacobs and Elderfield: J. Biol. Chem. **97**, 727 (1932).
(48) Jacobs and Elderfield: J. Biol. Chem. **100**, 671 (1933).
(49) Jacobs and Elderfield: J. Biol. Chem. **108**, 497 (1935).
(50) Jacobs and Elderfield: J. Biol. Chem. **113**, 611 (1936).
(51) Jacobs and Elderfield: J. Biol. Chem. **113**, 625 (1936).
(52) Jacobs, Elderfield, Grave, and Wignall: J. Biol. Chem. **91**, 617 (1931).
Jacobs and Elderfield: J. Biol. Chem. **91**, 625 (1931).
(53) Jacobs and Gustus: J. Biol. Chem. **74**, 795 (1927).
(54) Jacobs and Gustus: J. Biol. Chem. **74**, 829 (1927).
(55) Jacobs and Gustus: J. Biol. Chem. **78**, 573 (1928).
(56) Jacobs and Gustus: J. Biol. Chem. **79**, 553 (1928); **82**, 403 (1929); **88**, 531 (1930).
(57) Jacobs and Gustus: J. Biol. Chem. **86**, 199 (1930).
(58) Jacobs and Heidelberger: J. Biol. Chem. **81**, 765 (1929).
(59) Jacobs and Hoffman: J. Biol. Chem. **69**, 153 (1926); *cf.* Stoll and Renz: Enzymologia **7**, 362 (1939).
(60) Jacobs, Hoffmann, and Gustus: J. Biol. Chem. **70**, 1 (1926).
(61) Karrer, W.: Festschrift für E. C. Barell, p. 238 (Basel, 1936).
(62) Karrer, W.: Helv. Chim. Acta **26**, 1353 (1943).
(63) Katz: Pharm. Acta Helv. **22**, 244 (1947).
(63a) Katz: Helv. Chim. Acta **30**, 883 (1947).
(63b) Katz: Helv. Chim. Acta **31**, 993 (1948).
(64) Katz and Reichstein: Pharm. Acta Helv. **19**, 231 (1944).
(65) Katz and Reichstein: Helv. Chim. Acta **28**, 476 (1945).
(66) Katz and Reichstein: Pharm. Acta Helv. **22**, 437 (1947).
(67) Knowles, Fried, and Elderfield: J. Org. Chem. **7**, 383 (1942).
(68) Knowles, Kuck, and Elderfield: J. Org. Chem. **7**, 374 (1942).
(69) Koechlin and Reichstein: Helv. Chim. Acta **30**, 1673 (1947).
(70) Koenigs and Knorr: Sitzber. math-naturw. Abt. bayer Akad. Wiss. München **30**, 103 (1900).
(71) Kon: Chemistry & Industry **53**, 593, 956 (1934); Ann. Repts. Progress Chem. (Chem. Soc. London) **31**, 218 (1934).
(72) Lamb and Smith: J. Chem. Soc. **1936**, 442.
(73) Lang: Dissertation, Zurich, 1946.
(74) Linstead, Doering, Davis, Levine, and Whetstone: J. Am. Chem. Soc. **64**, 1985 (1942).

(75) Linville and Elderfield: J. Org. Chem. **6**, 270 (1941).

(76) Linville, Fried, and Elderfield: Science **94**, 284 (1941).
Fried, Linville, and Elderfield: J. Org. Chem. **7**, 362 (1942).

(77) McKenzie, McGuckin, and Kendall: J. Biol. Chem. **162**, 555 (1946).

(78) Mannich and Siewert: Ber. **75**, 737 (1942).

(79) Mannich and Siewert: Ber. **75**, 750 (1942).

(80) Marker, Crooks, Wagner, and Wittbecker: J. Am. Chem. Soc. **64**, 2089 (1942).

(81) Marker and Krueger: J. Am. Chem. Soc. **62**, 79 (1940).

(82) Marshall, Kuck, and Elderfield: J. Org. Chem. **7**, 444 (1942).

(83) Mason and Hoehn: J. Am. Chem. Soc. **60**, 2824 (1938); **61**, 1614 (1939).

(84) Mattox, Turner, Engel, McKenzie, McGuckin, and Kendall: J. Biol. Chem. **164**, 569 (1946).

(85) Meyer: Helv. Chim. Acta **29**, 718 (1946).

(86) Meyer: Helv. Chim. Acta **29**, 1580 (1946).

(87) Meyer: Helv. Chim. Acta **29**, 1908 (1946).

(88) Meyer: Helv. Chim. Acta **30**, 1976, (1947).

(89) Meyer: Helv. Chim. Acta **30**, 2024 (1947).

(90) Meyer and Reichstein: Helv. Chim. Acta **30**, 1508 (1947).

(91) Meystre and Miescher: Helv. Chim. Acta **27**, 1153 (1944).

(92) Mozingo, Wolf, Harris, and Folkers: J. Am. Chem. Soc. **65**, 1013 (1943).

(93) Neumann: Arch. exptl. Path. Pharmakol. **185**, 329 (1937).

(94) Neumann: Ber. **70**, 1547 (1937).

(95) Ott and Reichstein: Helv. Chim. Acta **26**, 1799 (1943).

(96) Paist, Blout, Uhle, and Elderfield: J. Org. Chem. **6**, 273 (1941).

(97) Plattner and Fürst: Helv. Chim. Acta **28**, 173 (1945).

(98) Plattner, Hardegger, and Bucher: Helv. Chim. Acta **28**, 167 (1945).

(99) Plattner and Heusser: Helv. Chim. Acta **28**, 1044 (1945).

(100) Plattner and Heusser: Helv. Chim. Acta **29**, 727 (1946).

(101) Plattner, Heusser, and Angliker: Helv. Chim. Acta **29**, 468 (1946).

(102) Plattner, Heusser, and Oeschger: Helv. Chim. Acta **29**, 253 (1946).

(103) Plattner and Lang: Helv. Chim. Acta **27**, 1872 (1944).

(104) Plattner, Meier, and Heusser: Helv. Chim. Acta **30**, 905 (1947).

(105) Plattner, Petrzilka, and Lang: Helv. Chim. Acta **27**, 513 (1944).

(106) Plattner, Ruzicka, and Fürst: Helv. Chim. Acta **26**, 2274 (1943).

(107) Plattner, Ruzicka, Heusser, and Angliker: Helv. Chim. Acta **30**, 385 (1947).

(108) Plattner, Ruzicka, Heusser, and Angliker: Helv. Chim. Acta **30**, 395 (1947).

(109) Plattner, Ruzicka, Heusser, and Angliker: Helv. Chim. Acta **30**, 1073 (1947).

(110) Plattner, Ruzicka, Heusser, and Meier: Helv. Chim. Acta **29**, 2023 (1946).

(111) Plattner, Ruzicka, Heusser, Pataki, and Meier: Helv. Chim. Acta **29**, 942 (1946).

(112) Plattner, Ruzicka, Heusser, Pataki, and Meier: Helv. Chim. Acta **29**, 949 (1946).

(113) Plattner, Ruzicka, and Pataki: Helv. Chim. Acta **28**, 389 (1945).

(114) Plattner, Segre, and Ernst: Helv. Chim. Acta **30**, 1432 (1947).

(115) Plattner and Uffer: Helv. Chim. Acta **28**, 1049 (1945).

(116) Press and Reichstein: Helv. Chim. Acta **25**, 878 (1942).

(117) Press and Reichstein: Helv. Chim. Acta **30**, 2127 (1947).

(118) Rabald and Kraus: Z. physiol. Chem. **265**, 39 (1940); German patent 723,224; Chem. Zentr. **1943**, **I**, 60.

(119) Reber and Reichstein: Helv. Chim. Acta **29**, 343 (1946).

(120) Reichstein and Fuchs: Helv. Chim. Acta **23**, 658 (1940).

(121) Reichstein and Katz: Pharm. Acta Helv. **18**, 521 (1943).

(122) Reichstein and Lardon: Helv. Chim. Acta **24**, 955 (1941).

(123) Reichstein and Montigel: Helv. Chim. Acta **22**, 1212 (1939).

(124) Reichstein and Reich: Ann. Rev. Biochem. **15**, 164 (1946).

(125) Reichstein and Rosenmund: Pharm. Acta Helv. **15**, 150 (1940).

(126) Rosenmund and Reichstein: Pharm. Acta Helv. **17**, 176 (1942).
(127) Ruzicka, Furter, and Thomann: Helv. Chim. Acta **16**, 333 (1933).
(128) Ruzicka, Hardegger, and Kauter: Helv. Chim. Acta **27**, 1164 (1944).
(129) Ruzicka and Muhr: Helv. Chim. Acta **27**, 503 (1944).
(130) Ruzicka, Plattner, and Balla: Helv. Chim. Acta **25**, 65 (1942).
(131) Ruzicka, Plattner, and Fürst: Helv. Chim. Acta **24**, 716 (1941).
(132) Ruzicka, Plattner, and Fürst: Helv. Chim. Acta **25**, 79 (1942).
(133) Ruzicka, Plattner, Fürst, and Heusser: Helv. Chim. Acta **30**, 694 (1947).
(134) Ruzicka, Plattner, and Heusser: Helv. Chim. Acta **25**, 435 (1942).
(135) Ruzicka, Plattner, and Heusser: Helv. Chim. Acta **27**, 186 (1944).
(136) Ruzicka, Plattner, and Heusser: Helv. Chim. Acta **27**, 1173 (1944).
(137) Ruzicka, Plattner, and Heusser: Helv. Chim. Acta **29**, 473 (1946).
(138) Ruzicka, Plattner, Heusser, and Ernst: Helv. Chim. Acta **29**, 248 (1946).
(139) Ruzicka, Plattner, Heusser, and Meier: Helv. Chim. Acta **30**, 1342 (1947).
(140) Ruzicka, Plattner, Heusser, and Pataki: Helv. Chim. Acta **29**, 936 (1946).
(141) Ruzicka, Plattner, and Pataki: Helv. Chim. Acta **25**, 425 (1942).
(142) Ruzicka, Plattner, and Pataki: Helv. Chim. Acta **27**, 988 (1944).
(143) Ruzicka, Plattner, and Pataki: Helv. Chim. Acta **28**, 1360 (1945).
(144) Ruzicka, Reichstein, and Fürst: Helv. Chim. Acta **24**, 76 (1941).
(145) Sarrett and Wallis: Ann. Rev. Biochem. **16**, 675 (1947).
(146) Schmiedeberg: Arch. exptl. Path. Pharmakol. **16**, 162 (1883); Ber. **16**, 253 (1883).
(147) Schmutz: Pharm. Acta Helv. **22**, 373 (1947).
(148) Schmutz and Reichstein: Pharm. Acta Helv. **22**, 167 (1947).
(149) Schmutz and Reichstein: Pharm. Acta Helv. **22**, 359 (1947).
(150) Schwartz, Katz, and Reichstein: Pharm. Acta Helv. **21**, 250 (1946).
(151) Shoppee: Ann. Rev. Biochem. **11**, 123 (1942); Ann. Repts. Progress Chem. (Chem. Soc. London) **43**, 225 (1946).
(152) Shoppee: Chemistry & Industry **1947**, 109.
(153) Shoppee: Helv. Chim. Acta **27**, 246, 426 (1944).
(154) Shoppee and Reichstein: Helv. Chim. Acta **23**, 975 (1940).
(155) Shoppee and Reichstein: Helv. Chim. Acta **25**, 1611 (1942).
(156) Smith: J. Chem. Soc. **1935**, 1305.
(157) Sorkin and Reichstein: Helv. Chim. Acta **29**, 1209 (1946).
(158) Sorkin and Reichstein: Helv. Chim. Acta **29**, 1218 (1946).
(159) Speiser and Reichstein: Experientia **3**, 281 (1947); Helv. Chim. Acta **30**, 2143 (1947); **31**, 622 (1948).
(160) Stavely and Bollenback: J. Am. Chem. Soc. **65**, 1285, 1290, 1600 (1943).
(161) Steiger and Reichstein: Helv. Chim. Acta **20**, 1040 (1937).
(162) Steiger and Reichstein: Helv. Chim. Acta **20**, 1164 (1937).
(163) Steiger and Reichstein: Helv. Chim. Acta **21**, 828 (1938).
(164) Steinegger and Katz: Pharm. Acta Helv. **22**, 1 (1947).
(165) Stoll *et al.*: Helv. Chim. Acta **17**, 641, 1334 (1934); **18**, 82, 120, 401, 644, 1247 (1935).
(166) Stoll, Kreis, and Hofmann: Z. physiol. Chem. **222**, 24 (1933).
(167) Stoll and Renz: Helv. Chim. Acta **24**, 1380 (1941).
(168) Stoll and Renz: Helv. Chim. Acta **25**, 43 (1942).
(169) Stoll and Renz: Helv. Chim. Acta **25**, 377 (1942).
(170) Stoll, Renz, and Helfenstein: Helv. Chim. Acta **26**, 648 (1943).
(171) Stoll, Suter, Kreis, Bussemaker, and Hofmann: Helv. Chim. Acta **16**, 703 (1933).
(172) Swern: J. Am. Chem. Soc. **69**, 1692 (1947).
(173) Torrey, Kuck, and Elderfield: J. Org. Chem. **6**, 289 (1941).
(174) Tschesche: Z. physiol. Chem. **222**, 50 (1933).
(175) Tschesche: Z. angew. Chem. **47**, 729 (1934).
(176) Tschesche: Z. physiol. Chem. **229**, 219 (1934).
(177) Tschesche: Ber. **68**, 7 (1935).

(178) Tschesche: Ber. **68**, 2252 (1935).
(179) Tschesche: Ber. **69**, 2368 (1936).
(180) Tschesche: Ber. **70**, 1554 (1937).
(181) Tschesche and Bohle: Ber. **69**, 793 (1936).
(182) Tschesche and Bohle: Ber. **69**, 2443 (1936).
(183) Tschesche and Bohle: Ber. **69**, 2497 (1936).
(184) Tschesche and Bohle: Ber. **71**, 654 (1938).
(185) Tschesche, Bohle, and Neumann: Ber. **71**, 1927 (1938).
(186) Tschesche and Haupt: Ber. **69**, 459 (1936).
(187) Tschesche and Haupt: Ber. **70**, 43 (1937).
(188) Uhle and Elderfield: J. Org. Chem. **8**, 162 (1943).
(189) Voss and Vogt: Ber. **69**, 2333 (1936).
(190) Wenner and Reichstein: Helv. Chim. Acta **27**, 24 (1944).
(191) Westphalen: Ber. **48**, 1064 (1915).
(192) Wieland and Benend: Ann. **554**, 1 (1943).
(193) Willstätter and Mayer: Ber. **41**, 2199 (1908).
(194) Windaus: Ber. **36**, 3752 (1903).
(195) Windaus and Haack: Ber. **63**, 1377 (1930).
(196) Windaus, Linsert, and Eckhardt: Ann. **534**, 22 (1938).
(197) Windaus and Schwarte: Ber. **58**, 1515 (1925).
(198) Windaus and Uibrig: Ber. **48**, 857 (1915).
Windaus: Ber. **49**, 1724 (1916).
(199) Windaus, Westphal, and Stein: Ber. **61**, 1847 (1928).
(200) Windaus and Zühlsdorff: Ann. **536**, 204 (1938).
(201) Winstein, Hess, and Buckles: J. Am. Chem. Soc. **64**, 2796 (1942).
(202) Woodward: J. Am. Chem. Soc. **64**, 72 (1942).

THE CHEMISTRY OF 4-HYDROXYQUINOLINES

ROBERT H. REITSEMA

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

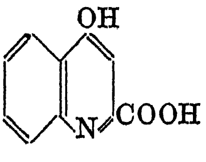
Received December 6, 1947

CONTENTS

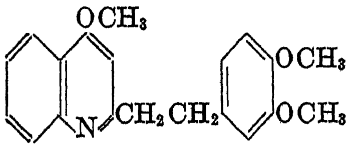
I. Introduction 43
II. Synthesis of 4-hydroxyquinolines 44
  A. From disubstituted aryl rings 44
  B. From ring closure of arylamine derivatives 46
    1. β-Anilinoacrylates 47
    2. β-Carbethoxy-β-anilinoacrylates 51
    3. α-Carbethoxy-β-anilinoacrylates 53
      (a) Syntheses from ethoxymethylenemalonic ester 54
      (b) Syntheses from amidines 55
      (c) Syntheses from imido chlorides 56
    4. Malonic acid anilides 56
    5. β-Anilinopropionates 57
  C. From 4-substituted quinolines 58
    1. From 4-chloroquinolines 58
    2. From 4-aminoquinolines 59
III. Properties of 4-hydroxyquinolines 60
  A. Structure 60
  B. Reactions at the 3-position 61
  C. Chlorination and subsequent reactions 63
IV. References 64

I. INTRODUCTION

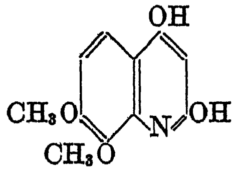
The search for new drugs useful in the treatment of malaria has resulted in the recognition of the value of 4-alkylaminoquinoline derivatives. The most general synthesis of these drugs has been through the 4-hydroxyquinolines. Consequently many chemists, especially those working for the Committee on Medical Research in the United States, recently have investigated the chemistry of 4-hydroxyquinolines. Another reason for the interest in 4-hydroxyquinolines is the occurrence of their derivatives in nature. These include kynurenic acid (I); angostura alkaloids such as cusparine, galipine (II), and 2-*n*-amyl-4-methoxyquinoline (72); and derivatives of *Rutaceae* such as 2,4-dihydroxy-7,8-dimethoxyquinoline (III) (55, 129).



I
Kynurenic acid



II
Galipine



III

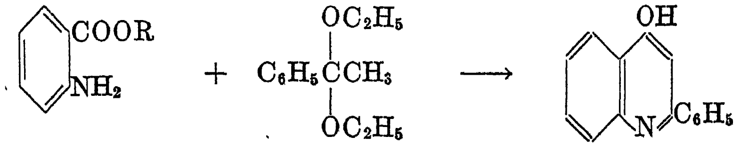
The preparation of 4-hydroxyquinolines has been divided into three classes. Syntheses in the first class are based upon quinoline formation from ortho-disubstituted aromatic compounds, those in the second class upon ring closure of arylamine derivatives, and those in the third class upon conversion of 4-chloro- and 4-amino-quinolines to 4-hydroxyquinolines.

Since 4-hydroxyquinolines possess interesting peculiarities in their reactions, a short discussion of their physical and chemical properties has been included.

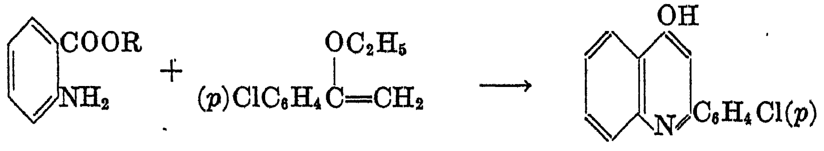
II. SYNTHESES OF 4-HYDROXYQUINOLINES

A. FROM DISUBSTITUTED ARYL RINGS

Anthranilic acid derivatives can be converted to 4-hydroxyquinolines by treatment with ketones. This method is particularly useful for preparing 2-aryl-4-hydroxyquinolines (84). Although an early report indicated that only a 3–5 per cent yield of 4-hydroxy-2-phenylquinoline was obtained from anthranilic acid and acetophenone (138), Fuson and Burness (64) reported that the anthranilic acid ester and the ketal of acetophenone gave an 84 per cent yield.

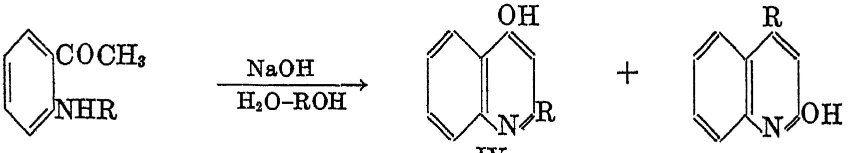


Owing to decarboxylation under the conditions of the reaction the free acid gave only a 50 per cent yield. The preference for the ester is not general however, since in the preparation of 4-hydroxy-3-methyl-2-phenylquinoline from the ketal of propiophenone, the free acid gave a 70 per cent yield while the ester gave only a 52 per cent yield. Further investigation of the reaction showed that p-chlorophenyl-α-ethoxystyrene was at least as useful as the ketal for the preparation of 2-(p-chlorophenyl)-4-hydroxyquinoline.



This reaction suggested that the ethoxystyrene may have been the intermediate in the reaction of the ketal.

o-Aminoacetophenones have been used instead of the anthranilates. The formyl derivative of o-aminoacetophenone yielded 4-hydroxyquinoline (IV, R = H) in very moderate yields (24, 36, 37). Acetylaminoacetophenone yielded 16–20 per cent of 2-methyl-4-hydroxyquinoline (IV, R = CH_3) in addition to a large amount of 2-hydroxy-4-methylquinoline (35).

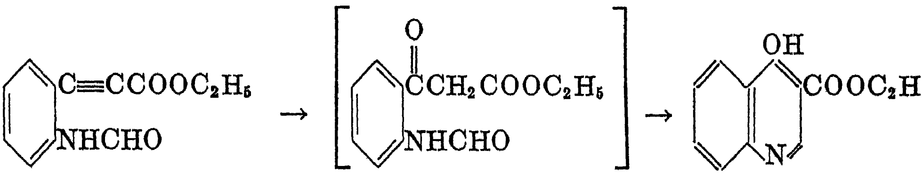


IV

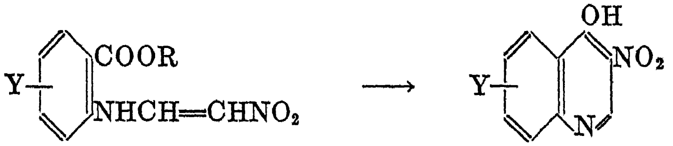
In a similar way IV has been prepared, where R was ethyl (190) or isopropyl (34). By similar methods other types of groups can be introduced in the 2-position. The oxamide derivative gave 2-carboxy-4-hydroxyquinoline (IV, R = COOH) (37), while the ethyl carbamate derivative gave 2,4-dihydroxyquinoline (IV, R = OH) (34). Extension to propiophenones gave 3-methyl-4-hydroxyquinolines (190).

Glyoxalation of *o*-nitroacetophenone and cyclization during reduction yielded 2-carboxy-4-hydroxyquinoline in 40–50 per cent yield (110). The 6-methoxy derivative also has been prepared by this method (5).

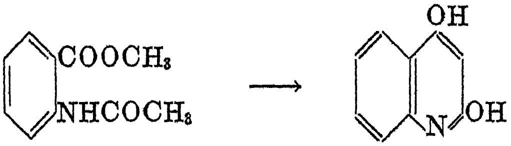
Some syntheses from less readily obtainable starting materials also have been reported. Ethyl *o*-formylaminophenylpropiolate produced 3-carbethoxy-4-hydroxyquinoline in 90 per cent yield (36, 37). This reaction has been postulated as occurring through the ketone.



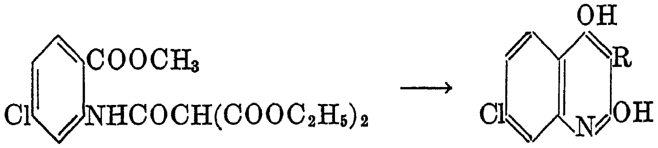
Closely related to this is the synthesis of dihydro-4-hydroxy-2-phenylquinoline from benzal-*o*-nitroacetophenone (119). From anthranilic acid derivatives and potassium methazoate were obtained 4-hydroxy-3-nitroquinolines (11, 45, 46, 133).



2,4-Dihydroxyquinolines constitute an important group often prepared by variations of the above methods. Treatment of methyl *N*-acetylanthranilate with sodium in xylene was reported to give a 60 per cent yield of 2,4-dihydroxyquinoline (33).



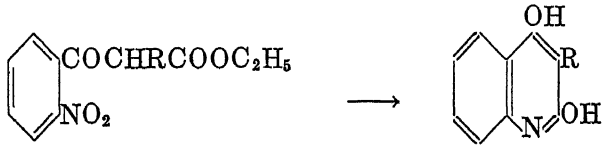
Later workers have been unable to obtain more than 28–40 per cent yields by this method (5, 30, 32). A still less satisfactory method employed methyl anthranilate and ethyl acetate with metallic sodium (61). One of the best methods of this type which had been reported by Koller (108) has been developed by Lutz and coworkers (117). The amide obtained from methyl 4-chloroanthranilate and malonic ester was cyclized, saponified, and decarboxylated to yield 7-chloro-2,4-dihydroxyquinoline in 72 per cent over-all yield.



R = $COOC_2H_5$, COOH, H.

Tetrahydroanthranilic ester gave a 71.5 per cent yield of the corresponding 5,6,7,8-tetrahydroquinoline (141). Sodium ethoxide has been used as the condensing agent in the reaction of methoxyanthranilyl chlorides with malonic ester to give undisclosed yields of 2,4-dihydroxy-5-, 6-, 7-, and 8-methoxyquinolines (21).

Bischoff has described the reduction of *o*-nitrobenzoylmalonates to 3-carbethoxy-2,4-dihydroxyquinoline (V) with tin and hydrochloric acid (4,22,66). In a similar reaction ethyl *o*-nitrobenzoylpropionate was reduced with phosphorus and hydriodic acid to 2,4-dihydroxy-3-methylquinoline (VI). Quinolines with methoxy groups in the benzenoid ring have also been reported (4, 140).

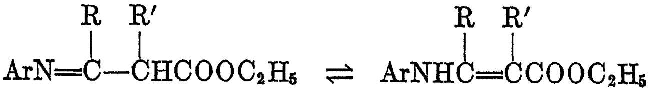


V: R = $COOC_2H_5$
VI: R = CH_3

The great advantage which the syntheses of this first class have in common is that no ring isomers are possible. The procedures are useful therefore to locate substituents exclusively in the 5- or 7-position of the quinoline ring. The main disadvantage aside from generally moderate yields is that the preparation of quinolines with substituents on the benzene ring often requires starting materials which are not readily available. The alternate syntheses from arylamines are preferable then, since only one substituent is needed for ring formation.

B. FROM RING CLOSURE OF ARYLAMINE DERIVATIVES

A large number of methods have been developed for the preparation of 4-hydroxyquinolines from arylamines possessing an unsubstituted ortho position. The intermediates in all cases can be considered as Schiff bases or as derivatives of acrylic acid.



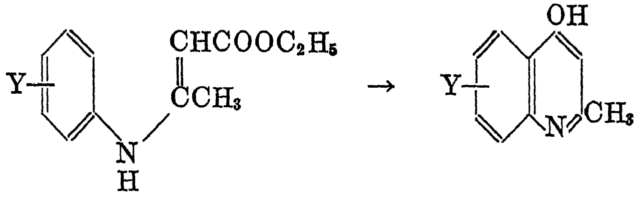
$$\mathrm{ArN{=}\overset{R}{\overset{|}{C}}{-}\overset{R'}{\overset{|}{C}}HCOOC_2H_5 \rightleftharpoons ArNH\overset{R}{\overset{|}{C}}{=}\overset{R'}{\overset{|}{C}}COOC_2H_5}$$

In this discussion this tautomerism will be ignored, and for clarity of nomenclature all intermediates will be regarded as β-arylaminoacrylates.

1. β-Anilinoacrylates

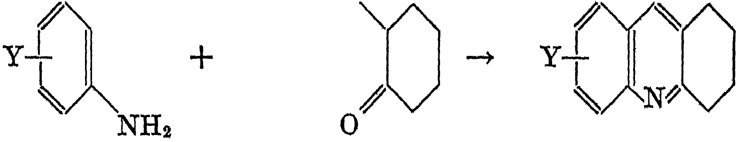
The Conrad–Limpach method is the most general reaction for the preparation of 2-alkyl-4-hydroxyquinolines. From arylamines and β-keto esters are obtained β-anilinoacrylates. When these are heated to around 250°C. ring closure occurs (48, 49, 50, 51).

$ArNH_2 + CH_3COCH_2COOC_2H_5 \rightarrow$



In the early work the cyclization was accomplished by heating the ester without a solvent and yields were very moderate. Limpach reported many years later that the yields in the cyclization were raised from below 30 per cent up to 95 per cent in many cases when an inert solvent such as mineral oil was used for the reaction (112, 113). Four to ten parts of solvent were used for each part of crotonate. Generally the cyclization was rapid. Heating for 20 min. at 240–250°C. was adequate to give 90–95 per cent yields of 4-hydroxy-2-methylquinoline.

Application of the Conrad–Limpach reaction to almost every type of arylamine has been made. The substituents in the benzene ring have included alkyl, nitro, halogen, and alkoxy groups. In table 1 will be found examples of 4-hydroxyquinolines prepared by this method. Some of the older work is included, despite lower yields to demonstrate the scope of the reaction. Often the yields of certain compounds are low even with a solvent, because of decomposition, as in the preparation of the 8-acetylaminoquinoline. A number of polycyclic derivatives also have been made. Aminocarbostyril (76), aminoacenaphthene (137), and 3-aminopyrene (187) have given polycyclic substituted 4-hydroxyquinaldines. Another interesting series was reported by Hughes and Lyons (85, 114) from 2-carbethoxycyclohexanone and arylamines.



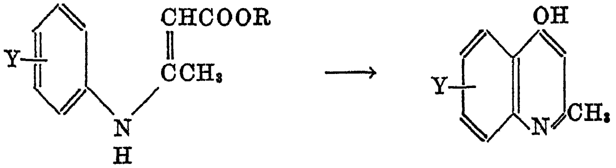
The arylamines used included 3,4-dimethoxyquinoline, 3- and 4-bromoanilines’ and 2-phenylaniline. The arylamine and keto ester were warmed at 100°C· and then added to mineral oil and heated at 250°C. for a few minutes.

The preparation of the anilinocrotonate has caused a good deal of confusion in the early literature. As Limpach has pointed out, the mixture of acetoacetic ester and arylamines gave crotonates at room temperature, while at 140–160°C. the anilide was formed (112).

It is apparent now that reports such as that of Knoor (101, 102) in which the free acid VII was postulated were in error. The amide was obtained, as Knoor himself indicated later (104). Hauser (79a) has discussed some factors governing the direction of this reaction.

TABLE 1

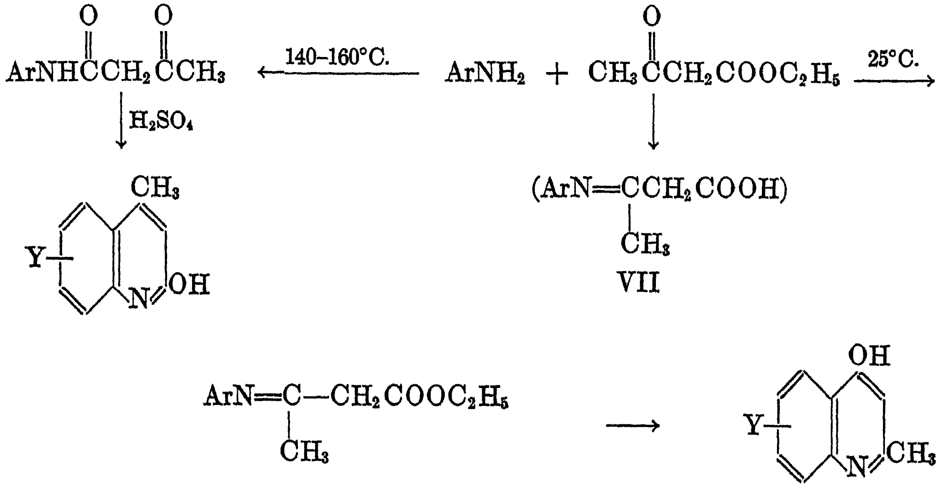
4-Hydroxyquinolines prepared by the Conrad-Limpach reaction



Y	YIELD FROM $ArNH_2$	SOLVENT	REFERENCE
	per cent		
H	—	None	(48, 175)
H	90–5	Mineral oil	(112)
6-CH_3	—	None	(51)
8-CH_3	27	None	(51)
5,7-$(CH_3)_2$	—	None	(51)
6,8-$(CH_3)_2$	—	None	(51, 84)
5,6,8-$(CH_3)_3$	50	None	(51)
5,6-Benzo	67	None	(51)
7,8-Benzo	90	Mineral oil	(70, 112, 113)
6-CH_3O	90	Mineral oil	(113)
6-CH_3O	61	None	(171)
6-C_2H_5O	90	Mineral oil	(112)
7(5)-OH	29*	Petrolatum	(134)
8-OH	50*	Paraffin oil	(136)
6,7-$(CH_3O)_2$	—	None	(114)
6,7-$(C_2H_5O)_2$	70	None	(114)
7,8-$(CH_3O)_2$	30	None	(78)
6-OH-8-$(CH_3)_2CH$	—	Vaseline oil	(85)
5-OH-8-Cl	—	Petrolatum	(134)
6-Cl	75	Paraffin oil	(98)
6-Br	56	Paraffin oil	(98)
7-Cl	72	Dowtherm	(146)
7-COOH-5,6-benzo	Quantitative	Mineral oil	(76)
5-CH_3CONH	30	Paraffin oil	(100)
6-CH_3CONH	79 (70*)	Paraffin oil	(87, 98, 161)
8-CH_3CONH	25*	Mineral oil	(124)
7,8-(3,4-Pyridyl)	60*	Mineral oil	(124)
7,8-(3,2-Pyridyl)	30*	Mineral oil	(124)

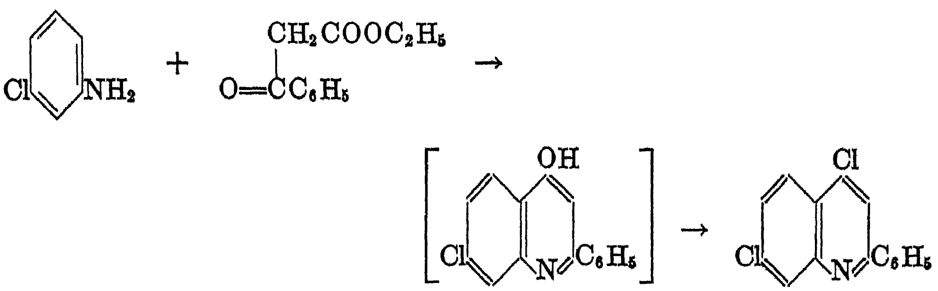
* Yield based on acrylate.

An investigation of various reaction conditions for the preparation of the crotonate has been reported by Coffey, Thompson, and Wilson (44). With very pure aniline 20 days were required for complete reaction, while commercial ani-


VII

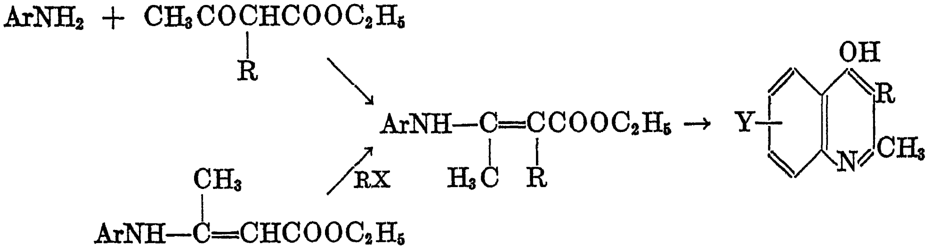
line required but a few days. One drop of strong acid caused the reaction to occur within 5 min. The rate of reaction was found to be in direct proportion to the acid strength. Although the reaction was very sensitive to acids, no effect was noticed with alkaline catalysts, contrary to some earlier reports. Some limitations to the preparation of crotonates have been noted, especially with *o*-, *m*-, and *p*-nitroanilines and derivatives such as *m*-nitro-*p*-toluidine, *p*-chloro-*o*-nitroaniline, 2,4-dinitroaniline, and *p*-methoxy-*o*-nitroaniline (44, 124).

The preparation of 2-aryl-4-hydroxyquinolines by the method of Conrad and Limpach, despite their report of the synthesis of 2-phenyl-4-hydroxyquinoline (50), has not proved as successful. Reaction of ethyl benzoylacetate with *m*-chloroaniline and treatment of the product with phosphorus oxychloride gave 3–5 per cent of 4,7-dichloro-2-phenylquinoline (58).

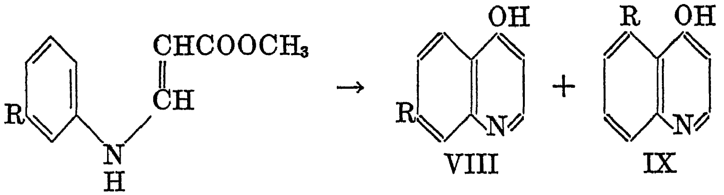


Ethyl β-methoxycinnamate in place of the ethyl benzoylacetate did not improve the yield. In this case at least, the use of anthranilic acid derivatives is superior.

Another class of compounds prepared by the Conrad–Limpach method is the 2,3-disubstituted 4-hydroxyquinolines. They have been prepared either from the substituted acetoacetic ester (98, 143, 180), or better by alkylation of the intermediate crotonate (111).



The Conrad–Limpach method has had only limited application to the synthesis of quinolines with an unsubstituted 2-position. The preparation of 4-hydroxyquinoline itself has been accomplished in 44 per cent yield from methyl β-anilinoacrylate (146).



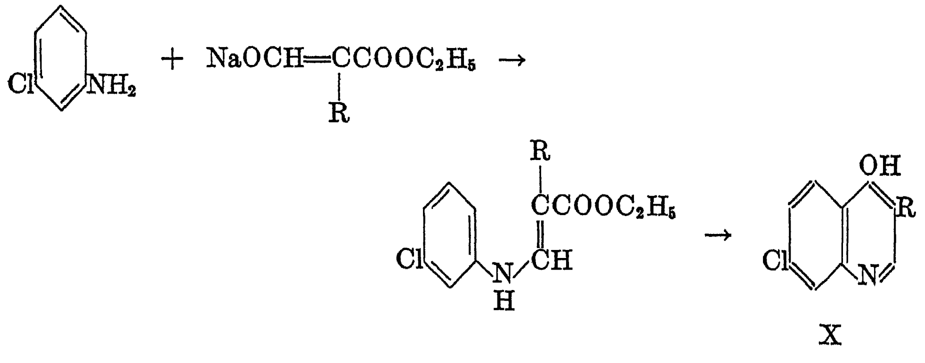
VIII IX

With *m*-chloroanilinoacrylate (R = Cl) 40 per cent of VIII and 10 per cent of IX were obtained. A large volume of solvent is necessary for the cyclization to avoid decomposition and production of diarylureas.

$$\mathrm{ArNHCH{=}CHCOOR} \xrightarrow{\mathrm{ArNH_2}} \mathrm{ArNHCONHAr} + \mathrm{CH_3CHO}$$

This side reaction parallels a similar decomposition of acetoacetic ester with arylamines (88, 103). Apparently this reaction confused Reissert (152, 153), and the physical properties he reported for the product he thought to be 4-hydroxyquinoline agree well with those for diphenylurea.

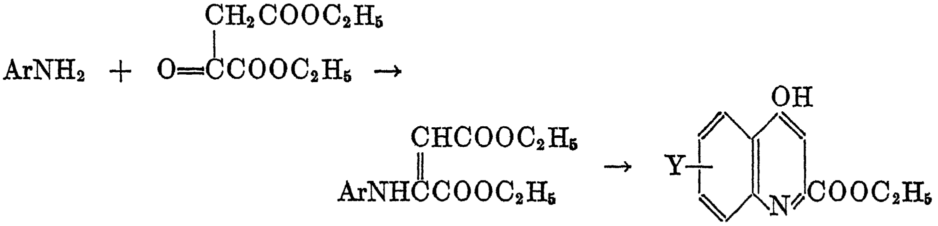
The formyl derivatives of esters other than ethyl acetate give 3-substituted quinolines. Thus, ethyl formylpropionate gave 7-chloro-3-methylquinoline (X, R = CH_3) in 60–65 per cent yield (146). The 3-phenyl derivative (X, R = C_6H_5) was prepared from ethyl α-formylphenylacetate in 36.5 per cent yield from *m*-chloroaniline (60) by an improvement on the original procedure of Wislicenus (189).



X

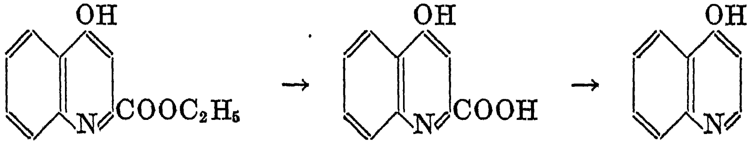
2. β-Carbethoxy-β-anilinoacrylates

The second general cyclization procedure for the synthesis of 4-hydroxyquinolines uses the intermediate acrylates formed from arylamines and oxalacetic esters. This method is identical with the normal Conrad–Limpach reaction except for the replacement of the methyl or other substituent in the 2-position with a carbethoxy group. As with the original Conrad–Limpach reaction, the cyclization was accomplished by heating the acrylate or mixture of arylamine and oxalacetic ester in an inert solvent at about 250°C.



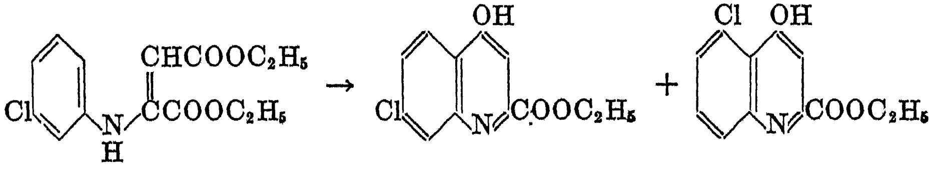
The acrylates were prepared in 78–95 per cent yields in methylene chloride or glacial acetic acid solution (177). For the cyclization solvent Dowtherm A was superior to mineral oil, since less decomposition occurred in that medium (179).

The usual investigation also required removal of the carbethoxy group by saponification and decarboxylation. Decarboxylation was carried out conveniently by heating the acid in Dowtherm.



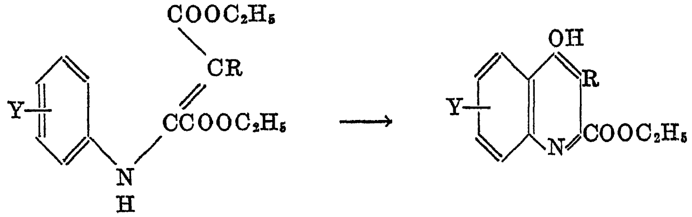
As indicated in table 2 the yields of the 2-carbethoxy-4-hydroxyquinolines are good. Some of the variations in yields result from basing the yield on either the intermediate acrylate or on the arylamine. The removal of the carbethoxy group is accomplished regularly in high yields. One disadvantage of the method is that widely varying conditions for cyclization and decarboxylation are necessary, depending upon the groups in the ring (159).

Table 2 also shows that 3-alkyl- or 3-aryl-quinolines are available. The majority of cases have a methyl group in the 3-position, although longer alkyl groups have been used. The substituents in the benzene ring are dependent upon the arylamine used. The demand for 7-chloro-4-hydroxyquinoline has led to an extensive investigation of the compounds produced by the cyclization of the *m*-chloroaniline derivative. In addition to the 7-chloroquinoline the 5-chloroquinoline was obtained.



The combined yield of the isomers based upon the arylamine was 56 per cent (182). This mixture was composed of nearly equal amounts of the 5- and 7-chloro isomers. *m*-Iodoaniline, however, gave nearly twice as much 7-iodo as 5-iodo derivative, indicating that the bulkiness of the group may be one factor

TABLE 2

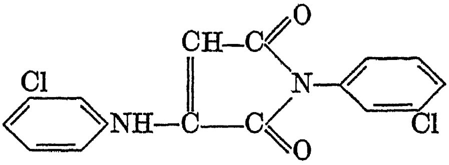


R	Y	YIELD FROM $ArNH_2$	YIELD FROM ACRYLATE	REFERENCE
		per cent	*per cent*	
H	H	61		(13, 38, 83, 133)
H	CH_3		87	(177)
H	5,6-Benzo		65	(131)
H	7,8-Benzo		89	(63)
H	6-CH_3O		85	(158, 162, 163)
H	8-CH_3O		85	(177)
H	8-C_2H_5		72	(177)
H	5-OH-8-Cl	—		(135)
H	5- and 7-Cl		32	(115, 182)
H	8-Cl		62	(177)
H	8-Br		59	(177)
H	5,7-Cl_2		55	(183)
H	5,7-Br_2		20	(183)
H	5,8-Cl_2		50	(183)
H	6,8-Cl_2		42	(183)
H	5-CH_3CONH	11		(97)
H	6-CH_3CONH	—		(99)
CH_3	6-CH_3		92	(176)
CH_3	6-CH_3O		97	(176)
CH_3	6-C_2H_5O		95	(176)
CH_3	7,(5)-CH_3O	62		(29)
CH_3	6-Cl		95	(176)
CH_3	6-Br	73	97	(29, 176)
CH_3	6-I		82	(179)
CH_3	5- and 7-Cl		97*	(178)
CH_3	5- and 7-Br		98*	(178)
CH_3	5- and 7-I		92*	(179)
CH_3	8-Cl	68		(29)
CH_3	8-I		89	(179)
CH_3	6-CH_3-7-Cl	60		(29)
CH_3	5-CH_3-8-Cl	62		(29)
$C_6H_{11}(CH_2)_3$	H	45–50		(13)

* Yield of combined isomers.

in determining the relative amounts of each isomer (179). Lisk and Stacey (115) found that in concentrated solution virtually none of the 5-chloro isomer was found, but the yield was prohibitively low. In dilute solutions about 40 per cent of the product was the 5-chloroquinoline, but at the same time the yield of the combined isomers was at a maximum.

In addition to the two ring isomers a by-product was isolated which proved to be a molecular compound of 7-chloro-4-hydroxyquinoline and *N*-(*m*-chlorophenyl)-α-(*m*-chloroanilino)maleimide (XI) (181).

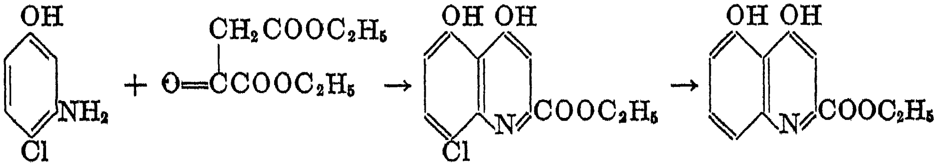


XI

The formation of XI indicates some decomposition of the acrylate, followed by reaction of the liberated *m*-chloroaniline with the β-carbethoxy ester to form the imide. It is apparent that the presence of excess arylamine will lower the yield of the quinoline appreciably, as has been shown also in the original Conrad–Limpach reaction (146).

The cyclization of the derivative of *m*-acetylaminoaniline is a rather surprising case. Only the 5-isomer was reported (97). Since the yield was very low, it is possible that the 7-isomer was formed but not isolated. This result is similar to the cyclization of the anil from *m*-acetylaminoaniline and acetoacetic ester related by one of the same authors (table 1) (100).

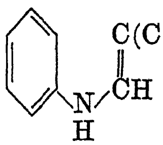
Musajo and Minchilli (135) obtained the pure 5-substituted derivative by by using the familiar device of blocking the most favored ortho position with a chlorine atom which was removed subsequently.

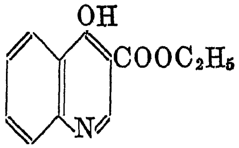


The 6-, 7-, and 8-substituted compounds are usually obtained in satisfactory yields from the *p*-, *m*-, and *o*-substituted anilines, although preparation of the 7-substituted quinolines by this method again involves a tedious separation from the 5-isomer.

3. α-Carbethoxy-β-anilinoacrylates

A very useful synthesis of 4-hydroxyquinoline and one which promises to be the most general was devised by Gould and Jacobs (76). The α-carbethoxy-β-anilinoacrylate esters were cyclized in mineral oil to 3-carbethoxy-4-hydroxyquinolines.





The cyclization is clean and results are generally uniform. This method was developed by Price and Roberts (148) for the synthesis of 7-chloro-4-hydroxyquinolines and has been applied by numerous groups to various arylamines.

(a) Syntheses from ethoxymethylenemalonic ester

Ethoxymethylenemalonic ester ("EMME") is prepared from diethyl malonate and ethyl orthoformate (39). This is the intermediate used by Gould and Jacobs and by most of the subsequent investigators for the preparation of the desired acrylates.

$$CH_2(COOC_2H_5)_2 + HC(OC_2H_5)_3 \rightarrow$$

$$C_2H_5OCH{=}C(COOC_2H_5)_2 \xrightarrow{ArNH_2} ArNHCH{=}C(COOC_2H_5)_2$$

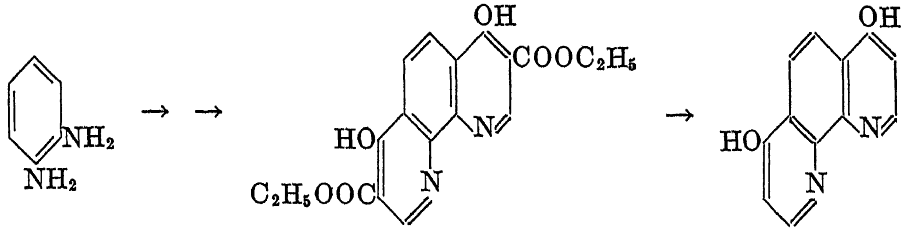
Fuson, Parham, and Reed (65) have prepared ethoxymethylenemalonic ester by condensing methyl diethoxyacetate and malonic ester and eliminating a molecule of ethanol.

$$(C_2H_5O)_2CHCOOCH_3 + CH_2(COOC_2H_5)_2 \rightarrow$$

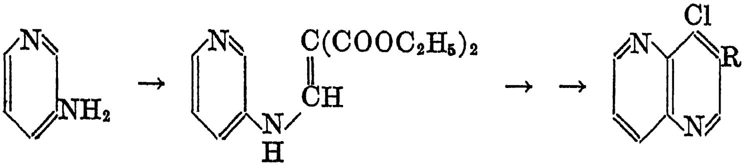
$$(C_2H_5O)_2CHCH(COOC_2H_5)_2 \rightarrow C_2H_5OCH{=}C(COOC_2H_5)_2$$

As in other reactions of the Conrad–Limpach type, the cyclization is carried out in refluxing diphenyl ether or Dowtherm. Mineral oil is a less desirable reaction medium. The saponification is generally accomplished in quantitative yield, and the acid is then decarboxylated by heating either dry or in the cyclization solvent. It has been noted that decarboxylation of certain nitroquinolines by the usual procedure never gave above 50 per cent yields and only small batches could be run. The preparation of the silver salt eliminated this difficulty (15). In another case impurities of the sodium salt caused completely altered behavior of the acid upon decarboxylation. Preliminary digestion with an excess of acid was found to be a remedy (109).

The generality of the method is shown by the fact that besides 4-hydroxyquinoline itself (77), 4-hydroxyquinolines have been prepared with substituents in the benzenoid ring such as the following: chloro (29, 148, 159, 184); fluoro and trifluoromethyl (173); methoxy and phenoxy (109, 159, 173); sulfide and disulfide (147); benzylmercapto, amino, and acetyl (149); and nitro (15, 77, 150, 159). The use of *o*-phenylenediamine yielded 4,7-dihydroxy-1,10-phenanthroline in an over-all yield of 58 per cent (172).



Other phenanthrolines have been obtained from the aminoquinolines (172). 4-Chloro-1,5-naphthryridine was obtained from 3-aminopyridine (1).



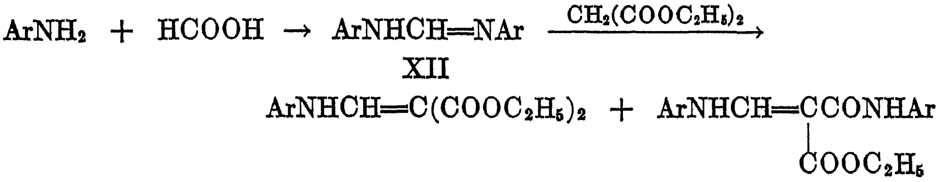
4-Hydroxy-6-sulfonamidoquinoline could not be prepared by this method, and although 6,6′-bis(4-hydroxyquinolyl) disulfide was obtained it could not be decarboxylated (14, 147).

Generally the synthesis gives mainly the 7-isomer from *m*-substituted anilines. *m*-Chloroaniline gave 15 per cent of the 5-isomer. However, *m*-fluoroaniline gave a large amount of the 5-isomer, and *m*-cyanoaniline gave only the 5-isomer (150).

A variation of the "EMME" synthesis was developed which used ethoxymethylenecyanoacetic ester rather than the malonate (144, 174). The product of the cyclization was a 3-cyano-4-hydroxyquinoline. The variation offered no advantage over the use of the malonate. Actually, the cyclization was slower, required a larger proportion of solvent, and yields from the cyclization were lower. Furthermore, the cyanoquinolines were much less tractable compounds than the esters.

b. Syntheses from amidines

Since ethyl orthoformate and consequently ethoxymethylenemalonic ester are relatively expensive, attempts have been made to find cheaper substitutes in the synthesis of α-carboxyanilinoacrylates. One of the more encouraging prospects is the decomposition of arylamidines with malonic ester itself (53, 144, 149, 174). Arylamidines (XII) have been prepared from formic acid and the arylamine in excellent yields.



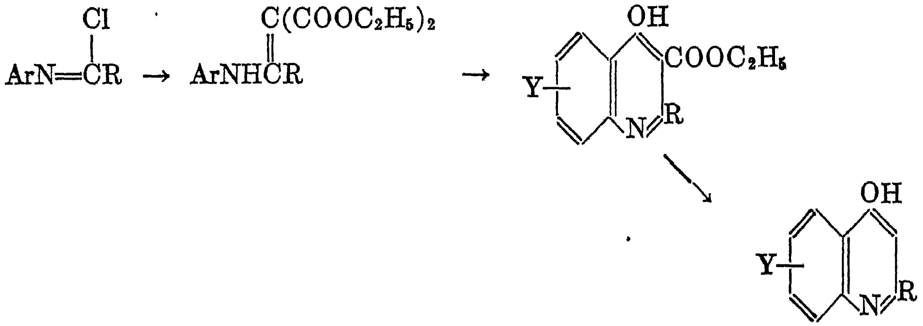
$$\mathrm{ArNH_2 + HCOOH \rightarrow \underset{XII}{ArNHCH{=}NAr} \xrightarrow{CH_2(COOC_2H_5)_2}}$$

$$\mathrm{\underset{XIII}{ArNHCH{=}C(COOC_2H_5)_2} + \underset{XIV}{ArNHCH{=}\underset{COOC_2H_5}{\underset{|}{C}}CONHAr}}$$

The formation of the anilide (XIV) occurred in 70 per cent yield when the reaction was carried out at 150–165°C. (144). By operating at 120°C. the yield of XIV was 10 per cent, while the desired acrylate XIII was formed in 38 per cent yield. Unreacted amidine could be recovered. This raised the yield of the acrylate to around 90 per cent (149). It was possible to cyclize XIV but, as with the nitrile, a much higher dilution was required.

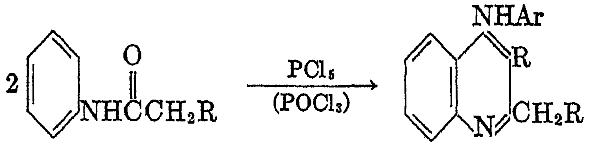
c. Syntheses from imido chlorides

A synthesis of 2-aryl-4-hydroxyquinolines which depended upon the cyclization of α-carboxy-β-aryl-β-arylaminoacrylates was described by Just (94, 95, 96). These acrylates were obtained from malonic ester and imido chlorides.



Seha and Fuchs (178) used this same procedure to prepare a series of 2-aryl-4-hydroxyquinolines with various substituents in the benzenoid ring. An improved yield followed from the use of toluene as the solvent and from the addition of one equivalent of malonic ester to reduce the amount of dicondensation product (169). In this manner an over-all yield of 30–40 per cent of various 2-aryl-4-hydroxyquinoline esters was obtained. The method has been used by Elderfield and coworkers for the synthesis of the 4-hydroxy-6- and 7-methoxy-2-phenylquinolines and 7-chloro-4-hydroxy-2-phenylquinolines (58). In the latter series the intermediate acrylate was not isolated but was cyclized directly to the quinoline in yields of 35–38 per cent.

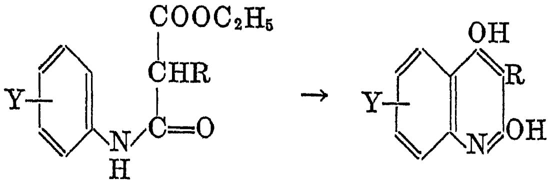
A closely related reaction of acylanilines has been reported in a number of papers (26, 27, 28, 79, 82, 169).



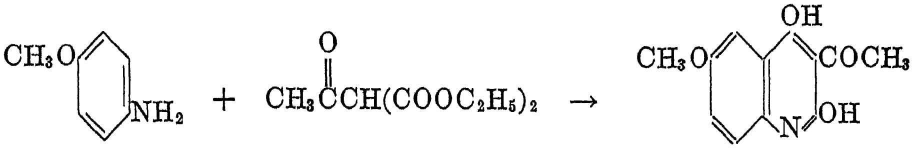
R = Cl, CH_3, C_2H_5, C_6H_5.

4. Malonic acid anilides

The most direct synthesis of 2,4-dihydroxyquinolines is by the cyclization of the half-anilides of malonic ester. The method for the same compounds described previously, using anthranilic acid derivatives, is usually preferable only for derivatives of *m*-substituted arylamines. The present method gives both the 5- and the 7-isomer although the 7-isomer predominates. Rugheimer used phosphorus pentachloride as a condensing agent and obtained chlorinated quinolines (164, 165, 166, 167). By heating the malonanilides at 250°C. the 2,4-dihydroxyquinolines have been obtained in over 80 per cent yields (17, 122).



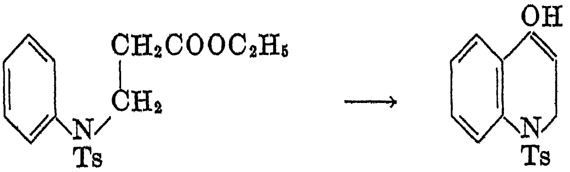
Nitrobenzene has been used as a solvent for the cyclization, and in this way a 63 per cent yield of 3-acetyl-2,4-dihydroxy-6-methoxyquinoline has been obtained (68, 185).



Baker, Lappin, and Riegel (16) found that earlier cyclization methods were not successful when applied to a mixture of cyclohexylpropylmalonic ester and aniline. The use of diphenyl ether as a reaction medium gave nearly quantitative yields of the desired 3-alkyl-2,4-dihydroxyquinoline from *p*-dimethylaminoaniline and cyclohexylmalonic ester or cyclohexylpropylmalonic ester. This modification was not suitable for *o*-nitroaniline or for cyclizations with allylmalonic ester or 3-diethylaminopropylmalonic ester.

5. *β-Anilinopropionates*

Some mention should be made of the attempts to prepare 4-hydroxyquinolines from β-anilinopropionates by cyclization and subsequent dehydrogenation. Clemo and Perkin (42, 43) found that the reaction of aniline and ethyl β-chloropropionate looked unpromising. However, they were able to cyclize the toluenesulfonyl derivative of the anilinopropionate. With phosphorus pentoxide a compound corresponding to 4-hydroxy-1-tosyl-1,2-dihydroquinoline was obtained. The work has been repeated by Backberg (6).

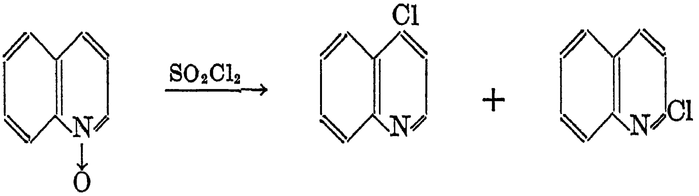


The product obtained by cyclization in phosphorus oxychloride contained chlorine, and Clemo and Perkin considered it to be 3-chloro-4-hydroxyquinoline. This gave 4-methoxyquinoline with sodium methoxide, and Diesbach and Kramer (54) interpreted this to indicate that actually the 4-chloro derivative was obtained. Since the anilinopropionates are readily available from arylamines and acrylic esters, Elderfield and coworkers have reinvestigated the reaction (57). These authors came to the conclusion that the reactions are obscure and information is still needed to interpret the reported reactions.

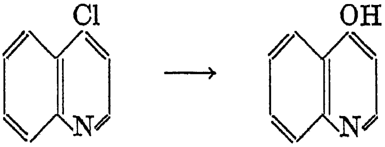
C. FROM 4-SUBSTITUTED QUINOLINES

1. From 4-chloroquinolines

The best synthesis of 4-chloroquinolines by far is the treatment of 4-hydroxyquinolines with phosphorus halides. Therefore the chloroquinolines would be of very little importance in the synthesis of 4-hydroxyquinolines if it were not for the reaction of quinoline *N*-oxides with sulfuryl chloride or phosphorus oxychloride reported by Meisenheimer (120).



Occasionally the conversion of 4-aminoquinolines to 4-haloquinolines by diazotization has gone very well, as in the preparation of 4-bromo-2-phenylquinoline (90). The halogen atom can then be replaced with the hydroxyl group. Bobranski (24) prepared 4-hydroxyquinoline in 69 per cent yield by treatment of the chloroquinoline with hydrochloric acid at elevated temperatures.



Similar acid hydrolyses have been reported by Skraup (170) and by Bachman and Cooper (10).

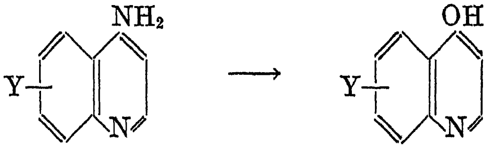
Further investigation of the reaction of quinoline *N*-oxide demonstrated that the reaction product obtained in 73 per cent yield consisted of about 62 per cent 4-chloroquinoline and 38 per cent 2-chloroquinoline (24, 25). The ratio of the isomers depended mainly upon substituents in the benzene ring (10). For instance, 6-methoxyquinoline gave 55 per cent of the 2-chloro- and 35 per cent of the 4-chloroquinoline, whereas 6-nitroquinoline gave 16 per cent of the 2-chloroquinoline and 56.5 per cent of the 4-chloroquinoline. Reaction conditions had little effect upon the ratio of isomers. Possible catalysts such as sulfuric, phosphoric, or acetic acid caused undesirable side reactions (10). Sulfuryl chloride was often superior to phosphorus oxychloride, but it failed to give a monochloro derivative of *m*-phenanthroline, while phosphorus oxychloride gave the 2-chloro derivative (97). By eliminating the possibility of isomers by blocking the 2-

position, very satisfactory yields of 2-aryl-4-chloroquinolines have been obtained by Gilman and coworkers (73, 74, 75). A methyl group also has been used to block the 2-position (47, 81). The Meisenheimer reaction could not be used to prepare the 4-chloro derivatives, for example, from 7-chloroquinoline (159), 8-nitroquinoline (77), 6-methoxy-8-nitroquinoline (77), 8-quinolinesulfonic acid (159), 8-methylquinoline (73), or 3-chloroquinoline (160). This lack of generality, the preparation of the oxides, and the separation of isomers decrease the usefulness of this reaction.

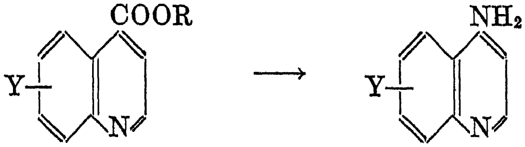
2. From 4-aminoquinolines

At present the most general synthesis of 4-aminoquinolines is from 4-chloroquinolines, which are best prepared from 4-hydroxyquinolines. Consequently the conversion of 4-aminoquinolines to the 4-hydroxyquinolines is of much less importance than formerly. In special cases, however, either primary or secondary 4-aminoquinolines are available and a brief survey of this source of 4-hydroxyquinolines would be of interest.

One of the earliest methods for the synthesis of 4-hydroxyquinolines was the treatment of 4-aminoquinolines with nitrous acid (18, 40, 41, 184, 188).



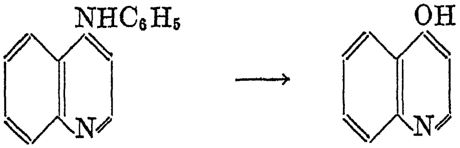
These 4-aminoquinolines were generally obtained from the corresponding carboxylic acid derivatives by a Hofmann rearrangement.



Recently, workers have developed the reaction and given more specific details than are available in the early literature. Renshaw and Friedman (156), for example, have obtained 4-aminoquinoline in 68 per cent yield from cinchoninic acid. 7-Methyl-4-aminoquinoline was prepared in 70 per cent yield (151). With dioxane as the solvent a 68 per cent yield of 4-amino-6-methoxyquinoline was obtained from the amide (59). The Curtius method has been used a great many times for the preparation of 4-aminoquinolines such as 4-aminoquinoline itself (31), 4-amino-2-phenylquinoline (89), and 4-amino-7-chloro-2-phenylquinoline (58).

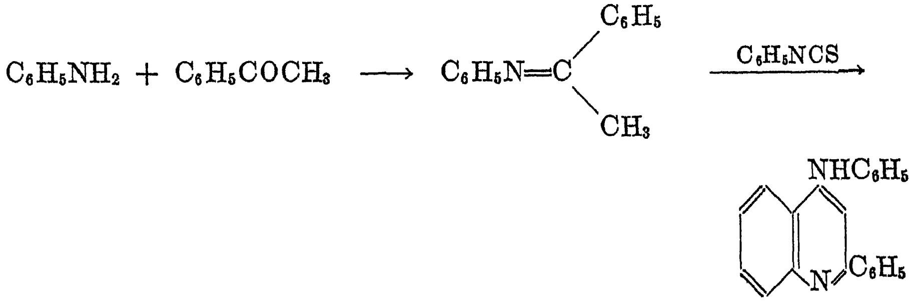
Isolated methods of preparing the primary aminoquinolines are known. Coupling of benzenediazonium chloride to 3-aminoquinoline and subsequent hydrogenolysis gave 3,4-diaminoquinoline (157). Bergstrom has developed the amination with potassium amide to give good yields of certain 2-substituted 4-aminoquinolines (18, 19).

4-Arylaminoquinolines are converted to 4-hydroxyquinolines much less readily than are the primary aminoquinolines. Alkali fusion has been used with undisclosed yields (56). Treatment with concentrated hydrochloric acid at 165°C. gave a 77 per cent yield of 4-hydroxyquinoline (27).

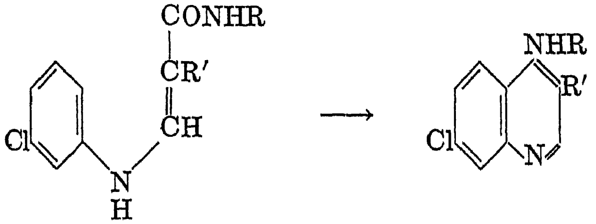


These arylaminoquinolines themselves are relatively inaccessible. One scheme, reported in a very long series of Russian papers by Dziewonski, Moszew, and others, made use of diarylthioureas and arylketones (56).

$$(C_6H_5NH)_2C{=}S \longrightarrow C_6H_5NH_2 + C_6H_5NCS$$



A more general synthesis with fair yields by the cyclization of amides has been reported recently by Price and Boekelheide (142). This type of reaction is common in the acridine series.

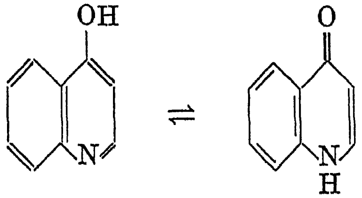


The method was useful where R′ was a nitrile or ester group and R was phenyl, chlorophenyl, butyl, hexyl, or cyanopentyl. If R contained a cyanoethyl group or any alkylaminoalkyl group, no quinoline was obtained.

III. Properties of 4-Hydroxyquinolines

A. STRUCTURE

In addition to ordinary α-naphthol resonance forms, two tautomeric forms can be written for 4-hydroxyquinoline, representing the compound as a phenol or as a ketone which would also be a vinylog of an amide.



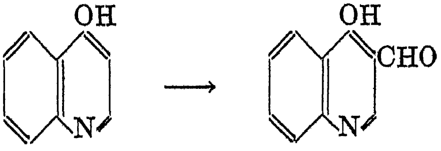
As expected, neither structure completely explains all the properties of the compound. The absorption spectra of 4-hydroxyquinoline would indicate that the ketonic form is predominant, as a result of the failure to obtain the shift in maxima in basic solution which would be expected were a phenolic group present (62). At the same time it was pointed out that definite assignment of the ketonic form could not be made if chemical reactions were considered. The compound behaves like a typical phenol in chemical reactions such as the Reimer–Tiemann reaction, and in formation of the 4-methoxyquinoline and 4-mercaptoquinoline. Bromination and other reactions at the 3-position also indicate the phenolic nature. The enolic structure is most useful in explaining the preparation of the 4-chloro derivative with phosphorus oxychloride and the generally enhanced acidic nature (3, 185). 4-Hydroxyquinolines, including 4-hydroxyquinoline itself, generally give colors with ferric chloride solutions.

The ketonic nature is shown in the formation of *N*-alkyl derivatives by reaction with alkyl halides. 4-Hydroxyquinoline cannot be reduced to the tetrahydro stage, although this is accomplished easily with the 5-, 6-, 7-, or 8-hydroxyquinoline (38). This again indicates a similarity to amides. Reduction of the benzoate of 4-hydroxyquinoline gave hydrogenolysis and subsequent formation of toluene and 4-hydroxyquinoline. Tin and hydrochloric acid were useful in the reduction of 3-carbethoxy-4-hydroxy-2-phenylquinoline to the tetrahydro stage (80). This carbethoxyquinoline is also peculiar in that alkylation at the 3-position is possible, indicating a greater contribution of the ketonic structure.

The problem of structure is the same as with 2-hydroxyquinolines and with 2- and 4-hydroxypyridines. The conclusion is that the ketonic character is predominant especially in physical tests, but that the phenolic character is present as indicated by certain chemical reactions.

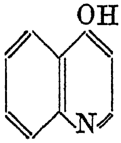
B. REACTIONS AT THE 3-POSITION

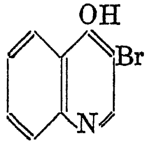
In a great many reactions with nitrogen heterocycles the position beta to the nitrogen is attacked. It is not surprising that if this is also ortho to a phenolic group some reactions occur quite readily. One example of this is the preparation of 4-hydroxy-3-quinolylaldehyde by the Reimer–Tiemann reaction (24, 52).



In a similar manner 4-hydroxy-2-methyl-3-quinolylaldehyde is prepared (52).

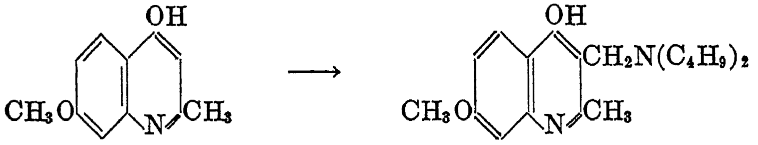
Bromination of 4-hydroxyquinolines gives 3-bromo-4-hydroxyquinolines in good yields (12, 160).





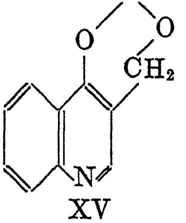
Chlorination produces a trichloro derivative. A di- and a tri-bromoquinaldine also have been described (49). Nitration of 4-hydroxy-2-methylquinoline has been reported to give the 6-nitro derivative (98). Other reports indicate that the 3-position also is attacked, as a result of the isolation of anthranilic acid from the oxidation of the nitrated quinoline (52, 98, 175).

The Mannich reaction again gives support to the aromatic structure. 4-Hydroxyquinolines give the 3-aminomethyl-4-hydroxyquinoline, as expected of phenols (73). It is well known that 2-methylquinolines will undergo a Mannich reaction to produce the 2-β-aminoethylquinolines. It is interesting therefore to note that 2-methyl-4-hydroxyquinoline gives the 3-aminomethyl derivative and the 2-methyl group is not affected (143).

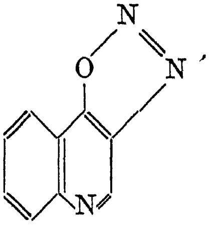


The proof of structure given for this compound makes it probable that the structure of a similar Mannich reaction product (69) is the 3-substituted quinoline rather than the indicated β-aminoethylquinoline. Methylolchloroacetamide also attacks 2,8-dimethyl-4-hydroxyquinoline in the 3-position (125). Further evidence that the 2-methyl group is not attacked is found in the failure of 2-methyl-4-hydroxyquinolines to condense with benzaldehyde as do 2-methylquinolines (123).

Closely related to the Mannich reaction and even stronger evidence for the existence of the enol form of 4-hydroxyquinolines is the formation of cyclic ethers (XV) by treatment with formaldehyde (XVI) (127). Similar to this are the cyclic azo derivatives of 3-amino-4-hydroxyquinolines (XVI) (52).



XV



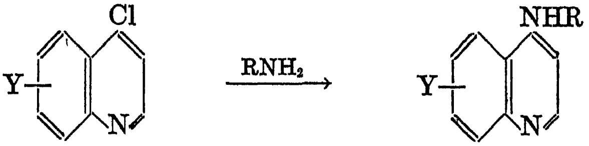
XVI

Coupling of groups such as diazo (52) and xyanthyl (128) also is known to occur at the 3-position. 4-Allyloxyquinolines behave as typical phenols and 3-allyl-4-hydroxyquinolines are produced by rearrangement (118).

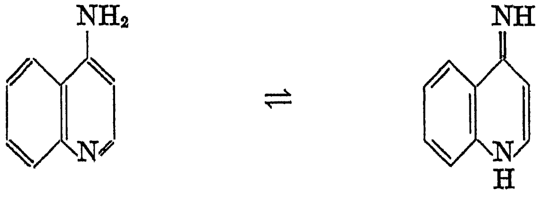
C. CHLORINATION AND SUBSEQUENT REACTIONS

Phosphorus oxychloride, phosphorus pentachloride, or a mixture of the two are the reagents most useful for the conversion of the 4-hydroxyquinoline to the 4-chloroquinoline. Phosphorus oxychloride in excess also can act as a solvent, or an inert solvent such as diphenyl ether may be used.

The chloroquinolines have a characteristic mouse-like odor. They are much lower melting than the hydroxyquinolines. The technique especially useful for the preparation of unsubstituted aminoquinolines is the treatment of the chloroquinoline in hot phenol with ammonia (29, 59, 145). The phenoxy compound, prepared easily by refluxing the chloroquinoline in phenol (9), may be the intermediate in this reaction, for the ethers can be converted to the aminoquinoline (86). Furthermore, no 4-aminoquinoline is produced if an inert solvent is used in place of phenol. The same method has been used to prepare some 4-alkylaminoquinolines, but a better method is to heat the 4-chloroquinoline with an excess of alkylamine. The latter method has been used most often for the large number of 4-alkylaminoquinolines reported recently. From 1929 to 1943, 172 derivatives of 4-aminoquinoline were prepared in the I. G. Farbenindustrie laboratories alone (23).



The 4-aminoquinolines present the same structure problems that the hydroxyquinolines do, and information about the aminoquinolines is useful for confirmation of conclusions about the hydroxyquinolines. Two extreme forms can be represented.



XVII XVIII

pK_a studies (3) give evidence for the quinoid form, since they show that 4-aminoquinolines are more basic than other aminoquinolines. The chemical evidence is more direct. Alkylation with alkyl halides leads to derivatives of XVIII (20), and the imino form can be isolated and hydrolyzed to the quinolone (145). On the other hand, formation of the sodium salt before treatment with the halide enables one to prepare derivatives of XVII. The dual possibilities of alkylation are additional reason for preparing alkylaminoquinolines from the 4-chloroquinoline rather than from the primary amine.

The reaction of 4-chloroquinolines with hydrazine is interesting, since in addition to the normal hydrazide at elevated temperature an isomer distinct from

3,4-diaminoquinoline is obtained (8, 107). Reduction of the azide derived from the hydrazide (7) or the phenylhydrazide (106) yields 4-aminoquinolines.

Other derivatives have been prepared from the 4-chloroquinolines. 4-Alkoxyquinolines are obtained by reaction with sodium methoxide (12, 105) or with sodium ethoxide (32). Many other ethers have been prepared from the chloroquinoline and sodium alkoxide or from the 4-hydroxyquinoline and the alkyl halide (92, 93, 116, 121, 132). With sodium bisulfite (161) or sodium sulfite (93, 139) the 4-sulfonic acids are produced in 84 per cent and 86 per cent yields. Sulfides are prepared from mercaptans (12, 52, 93) and substituted sulfonamides are prepared from primary sulfonamides (161).

IV. REFERENCES

(1) Adams, J., Bradsher, C., Breslow, D., Amore, S., and Hauser, C.: J. Am. Chem. Soc. **68**, 1317 (1946).
(2) Andersag, H., Breitner, S., and Jung, H.: U. S. patent 2,233,970; Chem. Abstracts **35**, 3771^7 (1941).
(3) Albert, A., and Goldacre, R.: Nature **153**, 467 (1944).
(4) Asahina, Y., and Nakanishi, S.: Ber. **63**, 2057 (1930).
(5) Ashley, J. N., Perkin, W. H., and Robinson, R.: J. Chem. Soc. **1930**, 382.
(6) Backberg, O. G.: J. Chem. Soc. **1933**, 618.
(7) Backberg, O. G.: J. Chem. Soc. **1938**, 1083.
(8) Backberg, O. G., and Friedman, C. A.: J. Chem. Soc. **1938**, 972.
(9) Backberg, O. G., and Marais, J. L. C.: J. Chem. Soc. **1942**, 381.
(10) Bachman, G. B., and Cooper, D. E.: J. Org. Chem. **9**, 302 (1944).
(11) Bachman, G. B., Welton, D. E., Jenkins, G. L., and Christian, J. E.: J. Am. Chem. Soc. **69**, 365 (1947).
(12) Baker, R. H., Albisetti, C. J., Dodson, R. M., Lappin, G. R., and Riegel, B.: J. Am. Chem. Soc. **68**, 1532 (1946).
(13) Baker, R. H., and Dodson, R. M.: J. Am. Chem. Soc. **68**, 1283 (1946).
(14) Baker, R. H., Dodson, R. M., and Riegel, B.: J. Am. Chem. Soc. **68**, 2636 (1946).
(15) Baker, R. H., Lappin, G. R., Albisetti, C. J., and Riegel, B.: J. Am. Chem. Soc. **68**, 1267 (1946).
(16) Baker, R. H., Lappin, G. R., and Riegel, B.: J. Am. Chem. Soc. **68**, 1284 (1946).
(17) Baumgarten, P., and Kargel, W.: Ber. **60B**, 832 (1927).
(18) Bergstrom, F. W.: J. Org. Chem. **3**, 233 (1938).
(19) Bergstrom, F. W.: J. Org. Chem. **3**, 424 (1938).
(20) Bergstrom, F. W.: Chem. Revs. **34**, 77 (1944).
(21) Berinzaghi, B., Muruzabal, A., Labriola, R., and Deulofeu, V.: J. Org. Chem. **10**, 181 (1945).
(22) Bischoff, C. A.: Ber. **22**, 386 (1889).
(23) Blanchard, K. C.: Report No. 246, Office of the Publication Board, Department of Commerce, Washington, D. C.
(24) Bobranski, B.: Ber. **69B**, 1113 (1936).
(25) Bobranski, B.: Ber. **71**, 578 (1938).
(26) Braun, J. von: Ber. **70B**, 979 (1937).
(27) Braun, J. von, and Heymons, A.: Ber. **63B**, 3191 (1930).
(28) Braun, J. von, Heymons, A., and Manz, G.: Ber. **64B**, 227 (1931).
(29) Breslow, D. S., Bloom, M. S., Shivers, J. C., Adams, J. T., Weiss, M. J., Yost, R. S., and Hauser, C. R.: J. Am. Chem. Soc. **68**, 1232 (1946).
(30) Brooker, L. G. S., and Smith, L. A.: J. Am. Chem. Soc. **59**, 67 (1937).
(31) Brydowna, W.: Roczniki Chem. **12**, 89 (1932); Chem. Abstracts **27**, 298^6 (1933).
(32) Buchmann, F. J., and Hamilton, C. S.: J. Am. Chem. Soc. **64**, 1357 (1942).

(33) CAMPS, R.: Arch. Pharm. **237**, 659 (1899).

(34) CAMPS, R.: Arch. Pharm. **239**, 591 (1901).

(35) CAMPS, R.: Ber. **32**, 3228 (1899).

(36) CAMPS, R.: Ber. **34**, 2703 (1901).

(37) CAMPS, R.: Z. physiol. Chem. **33**, 390 (1900).

(38) CAVALLITO, C. J., AND HASKELL, T. H.: J. Am. Chem. Soc. **66**, 1166 (1945).

(39) CLAISEN, L.: Ann. **297**, 77 (1897).

(40) CLAUS, A., AND FROBENIUS, W.: J. prakt. Chem. [2] **56**, 181 (1897).

(41) CLAUS, A., AND HOWITZ, H.: J. prakt. Chem. [2] **50**, 232 (1894).

(42) CLEMO, G. R., AND PERKIN, W. H.: J. Chem. Soc. **125**, 1608 (1924).

(43) CLEMO, G. R., AND PERKIN, W. H.: J. Chem. Soc. **127**, 2297 (1925).

(44) COFFEY, S., THOMPSON, J. K., AND WILSON, F. J.: J. Chem. Soc. **1936**, 856.

(45) COLONNA, M.: Gazz. chim. ital. **67**, 46 (1937).

(46) COLONNA, M.: Gazz. chim. ital. **69**, 684 (1939).

(47) COLONNA, M.: Boll. sci. facoltà chim. ind. Univ. Bologna **1941**, 86; Chem. Abstracts **37**, 3097 (1943).

(48) CONRAD, M., AND LIMPACH, L.: Ber. **20**, 944 (1887).

(49) CONRAD, M., AND LIMPACH, L.: Ber. **20**, 948 (1887).

(50) CONRAD, M., AND LIMPACH, L.: Ber. **21**, 521 (1888).

(51) CONRAD, M., AND LIMPACH, L.: Ber. **21**, 523 (1888).

(52) CONRAD, M., AND LIMPACH, L.: Ber. **21**, 1965 (1888).

(53) DAINS, F. B.: Ber. **35**, 2496 (1902).

(54) DIESBACH, H. DE, AND KRAMER, H.: Helv. Chim. Acta **28**, 1399 (1945).

(55) DEULOFEU, V., LABRIOLA, R., AND DELANGHE, J.: J. Am. Chem. Soc. **64**, 2326 (1942).

(56) DZIEWONSKI, K., AND MOSZEW, J.: Roczniki Chem. **13**, 530 (1933); Chem. Abstracts **28**, 1679 (1934). See also Chem. Abstracts **27**, 3937, 5331 (1933); **28**, 152, 1679 (1934); **29**, 1091, 6235, 6599 (1935); **30**, 1378 (1936); **31**, 1812, 1914 (1937); **32**, 4986 (1938); **33**, 608, 1711 (1939).

(57) ELDERFIELD, R. C., GENSLER, W. J., BEMBRY, T. H., KREMER, C. B., BRODY, F., HAGEMAN, H. A., AND HEAD, J. D.: J. Am. Chem. Soc. **68**, 1259 (1946).

(58) ELDERFIELD, R. C., GENSLER, W. J., BEMBRY, T. H., KREMER, C. B., HEAD, J. D., BRODY, F., AND FROHARDT, R.: J. Am. Chem. Soc. **68**, 1272 (1946).

(59) ELDERFIELD, R. C., GENSLER, W. J., BIRSTEIN, O., KREYSA, F. J., MAYNARD, J. T., AND GALBREATH, J.: J. Am. Chem. Soc. **68**, 1250 (1946).

(60) ELDERFIELD, R. C., AND WRIGHT, J. B.: J. Am. Chem. Soc. **68**, 1276 (1946).

(61) ERDMANN, H.: Ber. **32**, 3570 (1899).

(62) EWING, G. W., AND STECK, E. A.: J. Am. Chem. Soc. **68**, 2181 (1946).

(63) FOSTER, R. E., LIPSCOMB, R. D., THOMPSON, T. J., AND HAMILTON, C. S.: J. Am. Chem. Soc. **68**, 1327 (1946).

(64) FUSON, R. C., AND BURNESS, D. M.: J. Am. Chem. Soc. **68**, 1270 (1946).

(65) FUSON, R. C., PARHAM, W. E., AND REED, L. J.: J. Org. Chem. **11**, 194 (1946).

(66) GABRIEL, S.: Ber. **51**, 1500 (1918).

(67) GABRIEL, S., AND GERHARD, W.: Ber. **54B**, 1067 (1921).

(68) GERMAN PATENT 505,798; Chem. Zentr. **102, I**, 2679 (1931).

(69) GERMAN PATENT 597,907; Friedl. **16**, 2669 (1931).

(70) GIBSON, C. S., HARIHARAN, K. V., MENON, K. N., AND SIMONSEN, J. L.: J. Chem. Soc. **1926**, 2247.

(71) GILLIS, R., LIONS, F., AND RITCHIE, E.: J. Proc. Roy Soc. N. S. Wales **73**, 258 (1940); Chem. Abstracts **34**, 5846 (1940).

(72) GILMAN, H.: *Organic Chemistry*, Vol. II, p. 1208. John Wiley and Sons, Inc., New York (1943).

(73) GILMAN, H., CHRISTIAN, R. V., AND SPATZ, S. M.: J. Am. Chem. Soc. **68**, 979 (1946).

(74) GILMAN, H., AND SPATZ, S. M.: J. Am. Chem. Soc. **66**, 621 (1944).

(75) GILMAN, H., TOWLE, J. L., AND SPATZ, S. M.: J. Am. Chem. Soc. **68**, 2017 (1946).

(76) GOULD, R. G., AND JACOBS, W. A.: J. Am. Chem. Soc. **61**, 2890 (1939).

(77) Gouley, R. W., Moersch, G. W., and Mosher, H. S.: J. Am. Chem. Soc. **69,** (1947).

(78) Graves, J. N., Hughes, G. K., and Lions, F.: J. Proc. Roy. Soc. N. S. Wales 251 (1938); Chem. Abstracts **32,** 7461 (1938).

(79) Haen, J. D. R. de: German patent 532,397; Chem. Abstracts **26,** 151 (1932).

(79a) Hauser, C. R., Yost, R. S., Reynolds, G. A., Weiss, M. J., and Humphlett, W. J.: Abstracts of Papers presented at the 112th Meeting of the American Chemical Society, New York, September 15–19, 1947, page 172.

(80) Heeramaneck, V. R., and Shah, R. C.: Proc. Indian Acad. Sci. **5A,** 442 (1937); Chem. Abstracts **31,** 7432 (1937).

(81) Heller, G., Dietrich, W., and Reichardt, G.: J. prakt. Chem. **118,** 138 (1928).

(82) Heymons, A., and Rohland, W.: Ber. **66B,** 130 (1933).

(83) Hoffmann-La Roche, Inc.: German patent 575,534 (April 28, 1933).

(84) Huggill, H. P. W., and Plant, S. G. P.: J. Chem. Soc. **1939,** 784.

(85) Hughes, G. K., and Lions, F.: J. Proc. Roy. Soc. N. S. Wales **71,** 458 (1938); Chem. Abstracts **33,** 611 (1939).

(86) I. G. Farbenindustrie A.-G.: German patent 708,116; Chem. Abstracts **37,** 5084 (1943).

(87) Jacini, G.: Gazz. chim. ital. **71,** 53 (1941).

(88) Jadhav, G. V.: J. Indian Chem. Soc. **8,** 881 (1931).

(89) John, H.: Ber. **59B,** 1447 (1926).

(90) John, H.: J. prakt. Chem. **126,** 220 (1930).

(91) John, H.: J. prakt. Chem. **131,** 301 (1931).

(92) John, H., and Wunsche, E.: J. prakt. Chem. **119,** 43 (1928).

(93) John, H., and Wunsche, E.: J. prakt. Chem. **119,** 49 (1928).

(94) Just, F.: Ber. **18,** 2632 (1885).

(95) Just, F.: Ber. **19,** 1462 (1886).

(96) Just, F.: Ber. **19,** 1541 (1886).

(97) Kermac, W. O., and Tebrich, W.: J. Chem. Soc. **1945,** 375.

(98) Kermac, W. O., and Weatherhead, A. P.: J. Chem. Soc. **1939,** 563.

(99) Kermac, W. O., and Weatherhead, A. P.: J. Chem. Soc. **1940,** 1164.

(110) Kermac, W. O., and Webster, W.: J. Chem. Soc. **1942,** 213.

(101) Knorr, L.: Ber. **16,** 2593 (1883).

(102) Knorr, L.: Ber. **17,** 540 (1884).

(103) Knorr, L.: Ann. **236,** 69 (1886).

(104) Knorr, L.: Ber. **20,** 1397 (1887).

(105) Knorr, L., and Fertig, E.: Ber. **30,** 937 (1897).

(106) Koenigs, E., and Freund, J.: Ber. **74B,** 1085 (1941).

(107) Koenigs, E., and Loesch, V. M.: J. prakt. Chem. **143,** 59 (1935).

(108) Koller, G.: Ber. **60B,** 1108 (1937).

(109) Lauer, W. M., Arnold, R. T., Tiffany, B., and Tinker, J.: J. Am. Chem. Soc. **68,** 1268 (1946).

(110) Lawson, W., Perkin, W. H., Jr., and Robinson, R.: J. Chem. Soc. **125,** 626 (1924).

(111) Leonard, N. J., Herbrandson, H. F., and Van Heyningen, E. M.: J. Am. Chem. Soc. **68,** 1279 (1946).

(112) Limpach, L.: Ber. **64B,** 969, 970 (1931).

(113) Limpach, L.: German patent 455,387; Friedl. **16,** 2672 (1931).

(114) Lions, F.: J. Proc. Roy. Soc. N. S. Wales **71,** 242 (1938); Chem. Abstracts **32,** 7460 (1938).

(115) Lisk, G. F., and Stacy, G. W.: J. Am. Chem. Soc. **68,** 2686 (1946).

(116) Lockart, D., and Turner, E. E.: J. Chem. Soc. **1937,** 424.

(117) Lutz, R. E., Ashburn, G., Freek, J. A., Jordan, R. H., Leake, N. H., Martin, T. A., Rowlett, R. J., and Wilson, J. W.: J. Am. Chem. Soc. **68,** 1285 (1946).

(118) Mander-Jones, B., and Trikojus, V. M.: J. Proc. Roy. Soc. N. S. Wales **66**, 300 (1932); Chem. Abstracts **27**, 1350 (1933).
(119) Mannich, C., and Dannehl, M.: Ber. **71B**, 1899 (1938).
(120) Meisenheimer, J.: Ber. **59B**, 1848 (1926).
(121) Meyer, A., and Drutel, H.: Compt. rend. **204**, 1824 (1937).
(122) Meyer, A., and Heimann, P.: Compt. rend. **204**, 1204 (1937).
(123) Meyer, A., and Maurin, M.: Compt. rend. **200**, 931 (1935).
(124) Misani, F., and Bogert, M. T.: J. Org. Chem. **10**, 347 (1945).
(125) Monti, L.: Gazz. chim. ital. **67**, 624 (1937); Chem. Abstracts **32**, 4585 (1938).
(126) Monti, L., and Cirelli, V.: Gazz. chim. ital. **66**, 38 (1936); Chem. Abstracts **30**, 6380 (1936).
(127) Monti, L., Cirelli, V., and Rumano, B.: Gazz. chim. ital. **66**, 42 (1936); Chem. Abstracts **30**, 6372 (1936).
(128) Monti, L., and Delitala, M.: Gazz. chim. ital. **72**, 520 (1942); Chem. Abstracts **38**, 4599 (1944).
(129) Mookerjee, A., and Bose, P. K.: J. Indian Chem. Soc. **23**, 1 (1946); Chem. Abstracts **40**, 5750 (1946).
(130) Mueller, A. C., and Hamilton, C. S.: J. Am. Chem. Soc. **66**, 860 (1944).
(131) Mueller, A. C., and Hamilton, C. S.: J. Am. Chem. Soc. **65**, 1017 (1943).
(132) Murray, R. M., and Turner, E. E.: J. Chem. Soc. **1934**, 856.
(133) Musajo, L.: Gazz. chim. ital. **67**, 222 (1937); Chem. Zentr. **1937, II**, 2680.
(134) Musajo, L., and Minchilli, M.: Gazz. chim. ital. **70**, 301 (1940); Chem. Abstracts **35**, 3256 (1941).
(135) Musajo, L., and Minchilli, M.: Gazz. chim. ital. **71**, 762 (1941); Chem. Zentr. **1942, II**, 1459.
(136) Musajo, L., and Minchilli, M.: Ber. **74B**, 1839 (1941).
(137) Nair, S. V., and Simonsen, J. L.: J. Chem. Soc. **1926**, 3140.
(138) Niementowski, S.: Ber. **27**, 1394 (1894).
(139) Norton, T. R., Benson, A. A., Seibert, R. A., and Bergstrom, F. W.: J. Am. Chem. Soc. **68**, 1330 (1946).
(140) Overmeyer, C. J.: J. Am. Chem. Soc. **49**, 499 (1927).
(141) Prelog, V., and Szpilfogel, S.: Helv. Chim. Acta **28**, 1684 (1945).
(142) Price, C. C., and Boekelheide, V.: J. Am. Chem. Soc. **68**, 1246 (1946).
(143) Price, C. C., and Jackson, W. G.: J. Am. Chem. Soc. **68**, 1282 (1946).
(144) Price, C. C., Leonard, N. J., and Herbrandson, H. F.: J. Am. Chem. Soc. **68**, 1251 (1946).
(145) Price, C. C., Leonard, N. J., Peel, E. W., and Reitsema, R. H.: J. Am. Chem. Soc. **68**, 1807 (1946).
(146) Price, C. C., Leonard, N. J., and Reitsema, R. H.: J. Am. Chem. Soc. **68**, 1256 (1946).
(147) Price, C. C., Leonard, N. J., and Stacy, G. W.: J. Am. Chem. Soc. **69**, 855 (1947).
(148) Price, C. C., and Roberts, R. M.: J. Am. Chem. Soc. **68**, 1204(1946).
(149) Price, C. C., and Roberts, R. M.: J. Am. Chem. Soc. **68**, 1255 (1946).
(150) Price, C. C., Snyder, H. R., Bullitt, O. H., Jr., and Kovacic, P.: J. Am. Chem. Soc. **69**, 374 (1947).
(151) Ramsey, V. G., Baldwin, W. E., and Tipson, R. S.: J. Am. Chem. Soc. **69**, 67 (1947).
(152) Reissert, A.: Ber. **20**, 3105 (1887).
(153) Reissert, A.: Ber. **21**, 1362 (1888).
(154) Reissert, A.: Ber. **26**, 1758 (1893).
(155) Reitsema, R. H.: Unpublished data.
(156) Renshaw, R. R., and Friedman, H. L.: J. Am. Chem. Soc. **61**, 3320 (1939).
(157) Renshaw, R. R., Friedman, H. L., and Gajewski, F. J.: J. Am. Chem. Soc. **61**, 3322 (1939).

(158) Riegel, B., Albisetti, C. J., Lappin, G. R., and Baker, R. H.: J. Am. Chem. Soc **68**, 2685 (1946).

(159) Riegel, B., Lappin, G. R., Adelson, B. H., Jackson, R. I., Albisetti, C. J., Dodson, R. M., and Baker, R. H.: J. Am. Chem. Soc. **68**, 1264 (1946).

(160) Riegel, B., Lappin, G. R., Albisetti, C. J., Adelson, B. H., Dodson, R. M., Ginger, L. G., and Baker, R. H.: J. Am. Chem. Soc. **68**, 1229 (1946).

(161) Rubtsov, M. V., and Bunina, V. I.: J. Gen. Chem. (U.S.S.R.) **14**, 1128 (1944); Chem. Abstracts **40**, 7194 (1946).

(162) Rubtsov, M. V., and Lizgunova, M. V.: J. Gen. Chem. (U.S.S.R.) **13**, 697 (1943); Chem. Abstracts **39**, 704 (1945).

(163) Rubtsov, M. V., and Lizgunova, M. V.: U.S.S.R. patent 64,772; Chem. Abstracts **40**, 5776 (1946).

(164) Rugheimer, L.: Ber. **17**, 736 (1884).

(165) Rugheimer, L.: Ber. **18**, 2975 (1885).

(166) Rugheimer, L., and Hoffmann, R.: Ber. **17**, 739 (1884).

(167) Rugheimer, L., and Hoffmann, R.: Ber. **18**, 2979 (1885).

(168) Seka, R., and Fuchs, W.: Monatsh. **57**, 52 (1931).

(169) Shah, R. C., and Heeramaneck, V. R.: J. Chem. Soc. **1936**, 428.

(170) Skraup, Z. H.: Monatsh. **10**, 731 (1889).

(171) Slater, R. H.: J. Chem. Soc. **1931**, 107.

(172) Snyder, H. R., and Frier, H. E.: J. Am. Chem. Soc. **68**, 1320 (1946).

(173) Snyder, H. R., Frier, H. E., Kovacic, P., and Van Heyningen, E. M.: J. Am. Chem. Soc. **69**, 371 (1947).

(174) Snyder, H. R., and Jones, R. E.: J. Am. Chem. Soc. **68**, 1253 (1946).

(175) Stark, O.: Ber. **40**, 3425 (1907).

(176) Steck, E. A., Hallock, L. L., and Holland, A. J.: J. Am. Chem. Soc. **68**, 129 (1946).

(177) Steck, E. A., Hallock, L. L., and Holland, A. J.: J. Am. Chem. Soc. **68**, 132 (1946).

(178) Steck, E. A., Hallock, L. L., and Holland, A. J.: J. Am. Chem. Soc. **68**, 380 (1946).

(179) Steck, E. A., Hallock, L. L., and Holland, A. J.: J. Am. Chem. Soc. **68**, 1241 (1946).

(180) Stephen, J. M. L., Tomkin, I. M., and Walker, J.: Nature **156**, 629 (1945).

(181) Surrey, A. R., and Cutler, R. A.: J. Am. Chem. Soc. **68**, 514 (1946).

(182) Surrey, A. R., and Hammer, H. F.: J. Am. Chem. Soc. **68**, 113 (1946).

(183) Surrey, A. R., and Hammer, H. F.: J. Am. Chem. Soc. **68**, 1244 (1946).

(184) Tarbell, D. S.: J. Am. Chem. Soc. **68**, 1277 (1946).

(185) Vaughan, W. R.: J. Am. Chem. Soc. **68**, 324 (1946).

(186) Wenzel, F.: Monatsh. **15**, 453 (1894).

(187) Weizmann, M., and Bograchov, F.: J. Chem. Soc. **1942**, 377.

(188) White, H. C., and Bergstrom, F. W.: J. Org. Chem. **7**, 497 (1942).

(189) Wislicenus, W., Borner, K., Kurtz, P., and Bildhuber, E. A.: Ann. **413**, 206 (1917).

(190) Wohnlich, E.: Arch. Pharm. **251**, 526 (1913).

ADSORPTION AND PORE-SIZE MEASUREMENTS ON CHARCOALS AND WHETLERITES[1,2]

P. H. EMMETT

Mellon Institute, University of Pittsburgh, Pittsburgh 13, Pennsylvania

Received November 5, 1947

CONTENTS

I. Introduction 71
II. Measurements of surface areas 74
  A. Theory of the adsorption method and general application 74
  B. Measurement of surface areas of charcoals and whetlerites 76
III. Adsorption of water vapor 83
  A. Adsorption isotherms for various charcoals and whetlerites 83
  B. Rate of adsorption of water 85
  C. Nature of water adsorption on charcoal and whetlerites 87
IV. Pore size and pore-size measurements 93
  A. Molecular size as a criterion of pore size 93
  B. Pore size by applying the Kelvin equation to the adsorbates other than water 95
  C. Pore size from water adsorption and desorption isotherms 99
  D. Pore size from changes in surface area resulting from water uptake by charcoal 100
  E. Measurement of pore size by the high-pressure mercury method 103
V. Pore-size alteration 106
  A. Steaming without impregnation 107
  B. Hydrogenation without impregnation 108
  C. Partial combustion in nitrogen containing limited amounts of oxygen and no impregnants 109
  D. Influence of impregnants on steaming, hydrogenation, and partial oxidation 109
VI. Oxygen surface complexes on charcoals 112
  A. Introduction 112
  B. Oxygen adsorption by charcoals and its influence on their properties 113
    1. Oxygen pickup by charcoals 113
    2. Influence of oxygen treatment on the base and acid adsorptive properties 114
    3. Influence of surface complex on the adsorption of water vapor 116
    4. Influence of surface complex on the adsorption of ammonia and of hydrogen chloride 116
    5. Heat of binding of oxygen to carbon in the surface complex 117
  C. Gas evolution from charcoals as a function of the temperature to which they are heated 118
VII. Special surface coatings on charcoal 123
  A. Coating of charcoals with nitrogen 125

---

[1] This article has been approved for publication by the Public Information Division, Department of the Army.

[2] The term "whetlerite" was adopted during World War I for certain chemically treated charcoals which are especially effective for the removal of some of the poison gases. This name is used in a similar way throughout the present paper without, however, making any implications as to the nature of the materials that are added to the charcoal in preparing the modern whetlerites.

B. Treatment of charcoals with chlorine 126
C. Treatment of charcoals with sulfur 127
VIII. Relation between adsorption and molecular structure 128
A. Experimental data for the adsorption of gases on CWSN 19 128
B. Theory 128
IX. Retentitivity of charcoals 139
X. Chemisorption on the cupric oxide in type A whetlerites 139
XI. The structure of charcoal 140
A. X-ray structure work on charcoal 140
B. Microscopic studies 141
C. Electron microscope studies 141
D. Measurements of area and pore size 142
E. Chemical behavior of charcoal 142
F. Expansion of charcoals during adsorption 142
G. True density of carbon in charcoal 143
H. General conclusion as to structure 143
XII. References 144

The B.E.T. equation (29) applied to low-temperature adsorption isotherms of gases such as nitrogen appears to yield reliable surface areas for finely divided or coarsely porous solids. A modification of this equation for adsorption in narrow capillaries also seems to be reliable but is less susceptible to independent experimental verification.

Take-up of water vapor by activated charcoal may be best described as a combination of adsorption and capillary condensation. The rate of equilibration is comparatively low. Little take-up of water occurs at relative pressures lower than about 0.5. Desorption of water vapor from active charcoal is invariably accompanied by marked hysteresis, which usually disappears at a relative pressure of 0.35–0.4.

By measuring the decrease in surface area of a sample of charcoal as a function of the amount of water in the sample, it has been found possible to obtain a pore distribution for a large number of charcoals over the pore diameter range 16 Å. to about 500 Å. Pore-size distribution curves obtained in this way for several hundred charcoals have been found to join smoothly with those obtained by a mercury porosimeter for the range 1000–150,000 Å.

By suitable combination of steaming, hydrogenation or oxidation by air, with or without impregnation by oxides of iron, chromium, nickel, and copper, it has been found possible to tailor-make a given charcoal to a great variety of pore distributions.

Surface oxygen, hydrogen, or nitrogen complexes on charcoal differ in the temperature at which they can be removed from active charcoal by high-temperature degassing in the range 25–1000°C. As a rule, most of the carbon dioxide and water vapor are removed below 600°C., carbon monoxide in the range 600–900°C., and hydrogen and nitrogen between 600° and 1200°C. Chlorine and sulfur surface complexes are also tightly held by charcoal. These various coatings profoundly influence the adsorptive properties of charcoal.

A new theoretical treatment makes it possible to estimate whether a given gas will, at room temperature, be strongly, medium strongly, or weakly adsorbed by a charcoal, provided the polarizability, fundamental frequency, and critical temperature of the gaseous adsorbate are known and provided an adsorption isotherm of at least one known gas on the same charcoal is available.

Retentivity runs have shown that water vapor will decrease the adsorbability of all adsorbates insoluble in water, will have less influence on those slightly soluble in water, and will not cause a decrease in the equilibrium adsorption or retentivity of those gases that are completely miscible with water.

In attempts to measure the surface area of cupric oxide on type A whetlerites, it was found that hydrogen sulfide, phosphine, cyanogen chloride, boron trifluoride, hydrogen chloride, acetylene, and nitric oxide seem to react in excess of a monolayer even at room temperature; hydrogen sulfide, cyanogen chloride, boron trifluoride, and hydrogen chloride were especially active and seemed to react rapidly with the entire mass of cupric oxide. Carbon monoxide, sulfur dioxide, water, cyanogen, and ammonia are all chemisorbed in not to exceed a monolayer on the cupric oxide in the whetlerite.

The extensive research that has been carried out on charcoal still fails to establish with certainty the structure of active charcoal. It seems likely, however, that the charcoal is composed of tiny graphite-like platelets a few carbon atoms thick, but 20–100 Å. in diameter. These, when properly cross-connected, would form pores whose cross-sections would be more nearly rectangular than cylindrical.

I. INTRODUCTION

As part of a fundamental program designed to throw light on the surface area, pore size, and structural characteristics of an "ideal" charcoal, a great many measurements have been made during the last five years under the sponsorship and with the support of the Office of Scientific Research and Development.[3] The present report is an attempt to discuss critically and to summarize such work, taking due cognizance of the current concepts of area and pore-size measurements of porous solids. Such tables and figures as are incorporated have been selected to illustrate the nature of the work that has been carried out and the conclusions that have been reached. For more detailed accounts of the work and for presentation of the allied topics of charcoal preparation and of the kinetics of adsorption by a bed of charcoal, the reader is referred to the original articles which are now beginning to be published (46). For convenience of presentation and discussion, the work has been subdivided into ten sections.

Before summarizing the results obtained, it will be helpful to describe briefly the principal characteristics of the various charcoals mentioned in the paper. The charcoals were of four principal kinds: (*1*) those made by the zinc chloride process applied to sawdust; (*2*) those obtained from coal; (*3*) those made by the

---

[3] The individuals whose work is referred to throughout the present article and whose names appear on the government reports were working on NDRC projects located as follows:

The Johns Hopkins University: R. B. Anderson, P. H. Emmett, James Holmes, J. E. Jenkins, J. T. Kummer, C. V. Mace, and H. A. Pohl.

Northwestern University: M. Dole, I. M. Klotz, F. E. Blacet, W. C. Pierce, A. J. Juhola, T. Skei, J. W. Zabor, D. H. Volman, and G. J. Doyle.

Stanford University: P. A. Leighton.

University of Chicago: T. F. Young and S. Weller.

University of Delaware: A. P. Colburn.

University of Illinois: H. F. Johnstone, G. L. Clark, R. L. Le Tourneau, and P. G. Roach.

National Carbon Company: G. W. Heise, J. A. Slyh, M. Janes, N. M. Winslow, S. A. Taylor, and J. B. Sullivan.

University of Rochester: E. O. Wiig, J. J. Madison, J. F. Flagg, and (after July 1945) A. J. Juhola.

This list does not contain names of all of the technical personnel on the project but only those whose names actually appear on the restricted government reports quoted in this paper.

TABLE 1

Charcoals used in NDRC work and mentioned in figures, tables, or discussion

CHARCOAL NO.	RAW MATERIAL	ACTIVATION METHOD	PARTICLE DENSITY	MISCELLANEOUS DATA
CWSN S5	Hardwood sawdust	Zinc chloride		90% $ZnCl_2$ on dry weight basis; 1/16-in. extrusion
CWSN S5 (extracted with HF)	Hardwood sawdust	Zinc chloride		
CWSN 19	Hardwood sawdust	Zinc chloride	0.804	Ratio of $ZnCl_2$ to sawdust on dry weight basis = 0.9; 1/16-in. extrusion; primary calcination at 600°C. followed by rotary calcination at 850°C.
CWSN 19 TUC 45	Hardwood sawdust	Zinc chloride		CWSN 19 treated with oxygen at 400°C.
CWSN 19 TUC 46	Hardwood sawdust	Zinc chloride	0.53	CWSN 19 treated with oxygen at 400°C. to an 18.3% oxygen content
CWSN 19 TUC 742	Hardwood sawdust	Zinc chloride		CWSN 19 treated with oxygen at 400°C.
CWSN 22	Hardwood sawdust	Zinc chloride		Ratio of $ZnCl_2$ to sawdust = 0.9; 1/4-in. extrusion; calcined at 850°C.
CWSN 44	Hardwood sawdust	Zinc chloride	0.676	Ratio of $ZnCl_2$ to sawdust = 0.90; 1/16-in. extrusion
CWSN 45	Coconut shell	Carbon dioxide		Gas-activated coconut shell charcoal
CWSN 78	Hardwood sawdust	Zinc chloride		Ratio of $ZnCl_2$ to sawdust = 0.9; 1/16-in. extrusion; calcination at 600°C.
CWSN BX 110	Hardwood sawdust	Zinc chloride		1-in. extrusion; calcined at 600–900°C.; ratio of $ZnCl_2$ to sawdust = 1.1
CWSN 196 B1	Hardwood sawdust	Zinc chloride	0.534	
CWSN 196 B1X	Hardwood sawdust	Zinc chloride	0.570	Ratio of $ZnCl_2$ to sawdust = 1.10; 7-in. extrusion; oxidized; primary calcination at 600°C.; rotary recalcination at 850°C.; 1/2 hr. passage
CWSN 196 B1X TH 410	Hardwood sawdust	Zinc chloride	0.608	CWSN 196 B1X; 10 hr. heat treatment in nitrogen at 1100°C. to 4.5% weight loss
CWSN 196 B1X TH 427	Hardwood sawdust	Zinc chloride	0.574	CWSN 196 B1X impregnated with 5% Cr_2O_3; steamed to 18% weight loss at 950°C.; heated 10 hr. in nitrogen at 1100°C.
CWSN 203 AX	Hardwood sawdust	Zinc chloride		Ratio of $ZnCl_2$ to sawdust = 0.9

TABLE 1—*Continued*

CHARCOAL NO.	RAW MATERIAL	ACTIVATION METHOD	PARTICLE DENSITY	MISCELLANEOUS DATA
CWSN 291 AY1	Hardwood sawdust	Zinc chloride	0.619	Ratio of $ZnCl_2$ to sawdust = 1.10; 7-in. extrusion; dried at 200°C.; primary calcination at 700°C.; acid–caustic–water washed; rotary recalcination at 1000°C.
CWSN 291 AYY1	Hardwood sawdust	Zinc chloride	0.532	Same as 291 AY1 with additional tertiary sagger recalcination for 14 hr. at 1050°C.
CWSB X2	Nut shell	Steam		
CWSC 542	Sawdust	Steam		
CWSC 1242	Sawdust	Steam		
Coconut charcoal	Coconut shell			
MSA Grade 40	Probably coconut shell	Steam		
PCI P25	Coal	Steam		
PCI P58	Coal	Steam		
PCI P1042	Coal	Steam		
PCI P1042 (extracted with HF)	Coal	Steam		
PN 98	Coal	Steam	1.10	Powdered coal briquetted; air carbonized; steam activated for 90 min.
PN 106	Coal	Steam	0.93	Powdered coal briquetted; baked; steam activated at 1800°F. for 210 min.
PN 112	Coal	Steam	0.80	Same as PN 106 steam activated for 300 min.
RA 53	Coal	Steam	0.68	Powdered coal briquetted; air carbonized with final temperature at 850°F.; steam activated at 1800°F. for 200 min.
RC 79	Coal	Steam	0.66	Powdered coal briquetted; air carbonized; steam activated in rotary activator
NDRC SI B21	Saran	Steam		
NDRC SI B26	Saran	Not activated		
NDRC SI B42	Saran	Steam		
CFI "CC"	Coal			Activated charcoal from Colorado Fuel and Iron Co.; the coal was carbonized and activated directly without grinding and briquetting

steam activation of wood char; and (*4*) those obtained by the steam activation of coconut shell char. The list of charcoals, together with a brief description of them, is given in table 1.

II. MEASUREMENT OF SURFACE AREAS

A. Theory of the adsorption method and general application

During the last few years (55) a method has been developed for measuring the surface of the various porous and finely divided solids by means of adsorption isotherms taken near the boiling points of the gaseous adsorbates. Evidence has been obtained that the S-shaped isotherms such as shown in figure 1 correspond to the building up of a number of layers of adsorbed gas on the solid. Originally, it was suggested that the beginning of the long linear part of the isotherms (referred to as point *B*) represented the completion of the first layer and the beginning of the second (55). Later a theory was developed to take into account the formation of such multilayers in adsorption (29). It was shown (29) that the adsorption data can be plotted according to the equation:

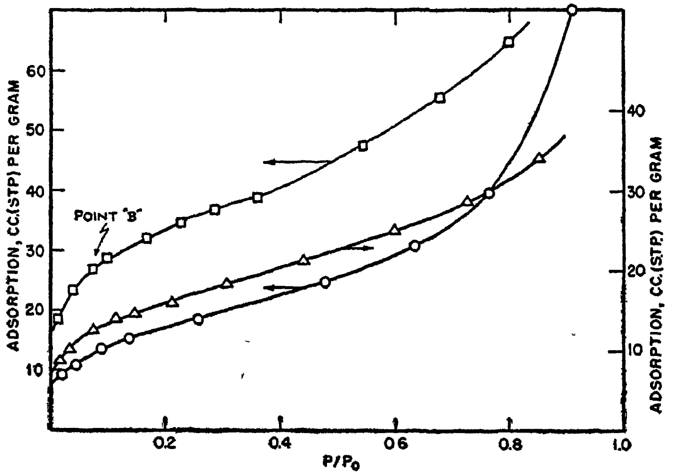


FIG. 1. Nitrogen-adsorption isotherms at −195°C.: ○, resin TR-2; △, P 33 carbon black; □, Wyex carbon black.

$$\frac{p/p_0}{V(1-p/p_0)} \doteq \frac{1}{V_m C} + \frac{(C-1)p}{V_m C p_0} \qquad (1)$$

to yield straight lines over the relative pressure range 0.05–0.35 (figure 2) from which V_m, the volume of gas required to form a monolayer on the adsorbent, can be evaluated. A simple multiplication of the number of adsorbate molecules in a monolayer by the average cross-sectional area of each adsorbate molecule will then yield a value for the surface area of the solid. V represents the volume of gas adsorbed (expressed at standard temperature and pressure) at the pressure p; p_0 is the liquefaction pressure of the adsorbate. C is a constant related to the heat of adsorption, E_1, by the equation:

$$C = \frac{a_1 b_2}{a_2 b_1} e^{(E_1 - E_L)/RT} \qquad (2)$$

where a_1, b_2, a_2, and b_1 are constants and E_L is the heat of liquefaction of the adsorbate. It has been found experimentally that for all isotherms for which C is the order of 50 or larger, the value of V_m obtained by plotting the data by equation 1 is in good agreement with point B, the beginning of the linear portions of the isotherm (figure 1).

The validity of surface-area calculations by equation 1 has been greatly strengthened recently by an independent approach to the problem by Harkins and Jura (75). By presaturating a non-porous, solid titanium dioxide with several layers of adsorbed water vapor and then measuring the heat of immersion in water of the titanium dioxide covered with adsorbed water, they are able to calculate directly the surface area of the solid. The heat of immersion expressed in ergs, divided by the surface energy (118.5 ergs per square centimeter of surface), yields an absolute value for the area of the finely divided titanium dioxide. By this direct method Harkins and Jura obtained a surface-area value of 13.8 sq. m. per gram for the adsorbent compared to 13.9 sq. m. per gram by use of equation 1. This latter value involved the assumption that the cross-sectional area of the nitrogen molecule is 16.2 Å.^{2}, as calculated from the density of liquid nitrogen. Harkins and Jura (76) also developed a new equation for plotting the adsorption data to yield directly a value for the surface area of finely divided and porous materials. It is based on the analogy between the surface phases formed in gas–solid systems and those formed on the surfaces of liquids (76). A somewhat similar method has also been suggested by Gregg (74) and applied by Maggs (115, 116, 117). The equation of Harkins and Jura involves a constant, the numerical value of which is fixed by calibration with titanium dioxide, using the surface-area value obtained by the heat of immersion. These alternative

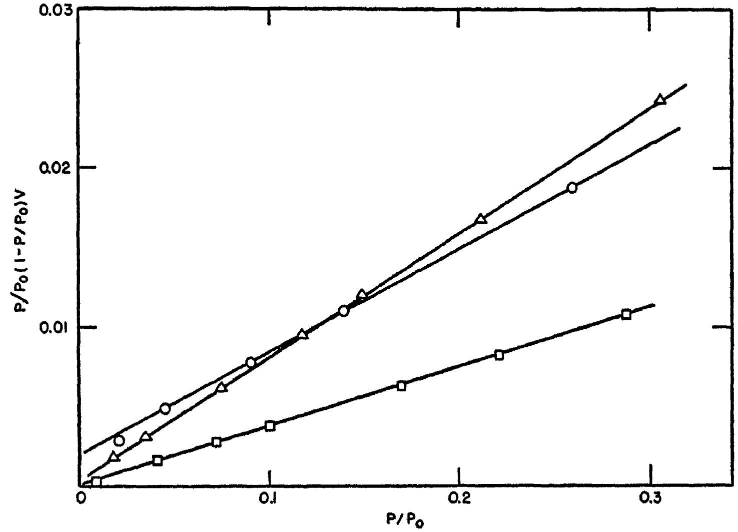


FIG. 2. Linear B.E.T. plots (29) of the isotherms from figure 1: ○, resin TR-2; △, P 33 carbon black; □, Wyex carbon black.

methods of plotting the low-temperature adsorption data need not be discussed in detail here (53). It will suffice to point out that, for a large number of porous and non-porous solids, there is good agreement between the plots of Harkins and Jura and those making use of equation 1.

Equation 1 has been applied to hundreds of different samples of adsorbents with apparent success (48, 49, 56, 76). S-shaped isotherms of the type (50) shown in figure 1 are invariably obtained if nitrogen is used as adsorbate and the measurements are made at about −195°C., provided the adsorbent does not have a large surface area located in small pores. Thus, it has been applied in measuring surface areas of carbon black (56), paint pigments (56), zinc oxide particles (56), metallic catalysts (29), metallic oxides (56), gel catalysts (29), and many other materials (48, 49). By using ethylene as an adsorbate at temperatures (−183°C.) at which the vapor pressure p_0 is $\sim$ 0.003 mm., Wooten and Brown (152) have succeeded in applying it even to areas as low as 100 sq. cm. Thermodynamic (31, 81) as well as kinetic derivations (29, 69) lead to equation 1, if one postulates that curves of the shape illustrated by figure 1 represent the building up of multilayers of adsorbed molecules on the surface. The higher the relative pressure, p/p_0, the greater the average statistical thickness of the adsorbed layer. In view of all of the experimental evidence thus far obtained, it may be concluded that by plotting low-temperature nitrogen-adsorption isotherms of the type shown in figure 1 according to equation 1, one can obtain reliable relative surface areas that are accurate to at least 5 per cent, and absolute values that are entirely reproducible on a given solid but might be in error by as much as 20 per cent, owing to uncertainties of molecular diameters and molecular packing.

B. Measurement of surface areas of charcoals and whetlerites

In the original paper by Brunauer, Emmett, and Teller (29) it was pointed out that if, for any reason, the maximum thickness to which adsorbed layers could build up on a surface is n molecular diameters, then the equation that one obtains to represent adsorption as a function of relative pressure (here designated for convenience as x rather than as p/p_0) is

$$V = \frac{V_m Cx[1 - (n + 1)x^n + nx^{n+1}]}{(1 - x)[1 + (C - 1)x - Cx^{n+1}]} \tag{3}$$

in which the symbols have the same meaning as in equation 1. Attention was also called to the fact that if $n = 1$, equation 3 reduces to the form

$$\frac{p}{V} = \frac{p_0}{CV_m} + \frac{p}{V_m} \tag{4}$$

which is identical with the Langmuir equation.

For materials such as charcoal having a large number of very fine pores, n is conveniently interpreted as one-half the diameter (expressed as number of molecular diameters) of the pores, cracks, or crevices in which the adsorption occurs. It has been shown by Deitz and Gleysteen (43) and by Joyner, Weinberger, and Montgomery (88) that equation 3 can be applied successfully to the adsorption isotherms for a number of materials having so many fine pores as not to fall in the class represented by equation 1. Figure 3 contains a number of isotherms that follow equation 3 over the relative pressure range 0.1–0.4; the values of n, C, and V_m that give a good fit to the equation are also indicated.

Pickett (129) and, more recently, Anderson (12) have questioned equation 3 on the grounds that at relative pressures of 1.0 it does not postulate the complete filling of a crevice with adsorbate but a partial filling equal to

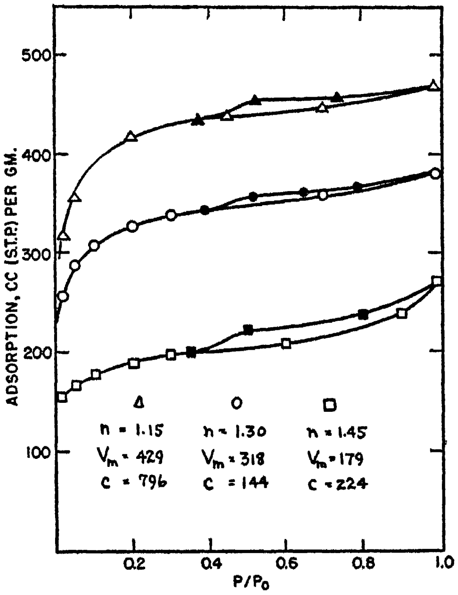


FIG. 3. Nitrogen-adsorption isotherms at −195°C. for charcoal data taken from paper by Joyner, Weinberger, and Montgomery (88).

$$(n+1)\Big/2\left(1+\frac{1}{Cn}\right)$$

They carried out the summation up to n layers in a manner different from that employed by Brunauer, Emmett, and Teller (29) and arrived at an equation of the form:

$$V = \frac{V_m Cx(1-x^n)}{(1-x)(1-x+Cx)} \tag{5}$$

The derivation can be carried out in a number of ways; it is, for example (146), the result obtained if one assumes that the rate of escape of molecules from the top layer in a capillary is proportional to θ, the fraction of the surface covered by absorbed molecules and also to $1 - p/p_0$. The rate of evaporation thus is assumed to approach zero as p/p_0 approaches unity. This equation has the advantage of representing the complete filling of the capillaries at a relative pressure of 1; however, the value of V_m obtained by equation 5 is substantially the same as that obtained by equation 3. Hence, Pickett and Anderson's suggestions are much more pertinent to the question of pore volume than to that of surface area. Furthermore, equation 3 and not equation 5 is obtained by a statistical mechanical (80) or thermodynamic derivation. It seems probable, therefore, that equation 3 may be relied upon for surface-area measurements of materials having small pores, even though there may be some question as to the course followed by the adsorption isotherm near saturation.

It should be made clear at the start that the measurement of the surface area is much less exact for a material such as charcoal, chabazite, and some gels, having pores which in size approach molecular dimensions, than for non-porous substances or those having large pores. For example, equations 1 and 3 have both been derived on the assumption that the adsorption is taking place on cracks having plane parallel walls. Without doubt, the actual pores and capillaries of many materials have no such simple structure. Indeed, it may be that frequently the small pores might better be described as cylinders or cones rather than cracks or crevices. A further cause of uncertainty arises from the lack of any good independent means of checking the area of substances having pores of molecular dimensions. There is no way of resolving these uncertainties at the present time; their existence, however, should always be kept in mind.

The detailed calculation of surface areas by equation 3 was not used in most of the work that was done by the National Defense Research Committee on charcoal during the war, because the calculations involved were too time-consuming (64). For most samples, equation 4 has been employed; in a few instances (90) even equation 1 has been used. However, as pointed out by Joyner and coworkers (88), the use of equation 4 for adsorption isotherms for a sample for which $n = 1.5$ yields an area value about 15 per cent higher than obtained by using equation 3, whereas employing equation 1 for plotting the adsorption data will yield a value 18 per cent lower than that obtained by equation 3. The exact ratios between the areas obtained by equations 3 and 4 as a function of the value of n are shown in figure 4, taken from their paper. Accordingly, even though equations 1 and 4 have been used extensively as approximations for measuring the surface areas of charcoal, nevertheless, in the writer's opinion, the most reliable surface-area values by nitrogen adsorption are obtained by fitting the adsorption isotherms to equation 3 and evaluating V_m after determining the values of n and C that are needed to fit the data to the equation over the range 0.1–0.4 relative pressures. The area values obtained for charcoals by equation 4 are probably upper limits, and those obtained by equation 1 represent lower limits to the correct areas.

The numerical value of the surface area that one will obtain by the use of equation 1, 3, or 4 will, of course, depend markedly on the gas used as adsorbate. Even on non-porous or coarsely porous solids there seems to be some indication (20, 42) that surface areas obtained by large molecules are a little smaller than those obtained by smaller molecules if the molecular cross-sections are calculated from the density of liquids in the usual way (55). For materials with fine pores this effect of molecular size is, of course, much magnified. For example, it has been known for many years that chabazite, when properly dehydrated, will exhibit a screening action on molecules larger than ethane (138). Indeed, it has been shown that it is possible to make the pores so small in dehydrated chabazite as to permit the adsorption of hydrogen molecules but not nitrogen (57), nitrogen but not butane (57), and straight-chain hydrocarbons but not branched-chain hydrocarbons (18, 19). On charcoal similar screening effects are very much in evidence. On a charcoal such as Saran (65), shown in figure 5, the adsorption of isoöctane is only one-twelfth as large as it should be if nitrogen and isoöctane were being adsorbed on the same pore walls (65). On charcoals with larger pores (figure 6), such as are produced by more extensive activation, the screening is still in evidence but much less pronounced. A plot of surface area (calculated by equation 4) as a function of molecular size[4] is shown in figure 7 for CWSN 19.

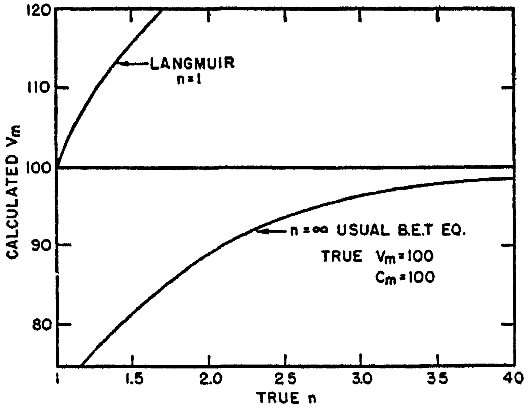


FIG. 4. Curves showing the errors involved in using equation 1 or equation 4 for measuring surface areas for charcoals for which the n values of equation 3 range from 1 to 4.

As indicated, a surface-area value for charcoal will, in general, be smaller the larger the molecule employed for the adsorption measurements. The influence of molecular size on the apparent surface area of a series of charcoals is well illustrated by table 2, compiled from data published by Fineman, Guest, and McIntosh (68). The six samples of coconut shell charcoal were steam activated for different periods of time, as indicated in column 2. For the molecular cross-sectional area of butane they used two values of (*a*) 32.1 Å.^{2} and (*b*) 48.0 Å.^{2} (55). It is apparent that in the early stages of activation nitrogen isotherms yield a much larger area than butane isotherms; the areas by the two gases come closer

---

[4] The molecular cross-sectional areas used in calculating the surface areas in figure 7 were obtained from (55) the equation

$$\text{Molecular area} = 4(0.866)\left[\frac{M}{4\sqrt{2}\,A d_l}\right]^{2/3} \qquad (6)$$

where M is the molecular weight, A is Avogadro's number, and d_l is the density of the liquefied adsorbate.

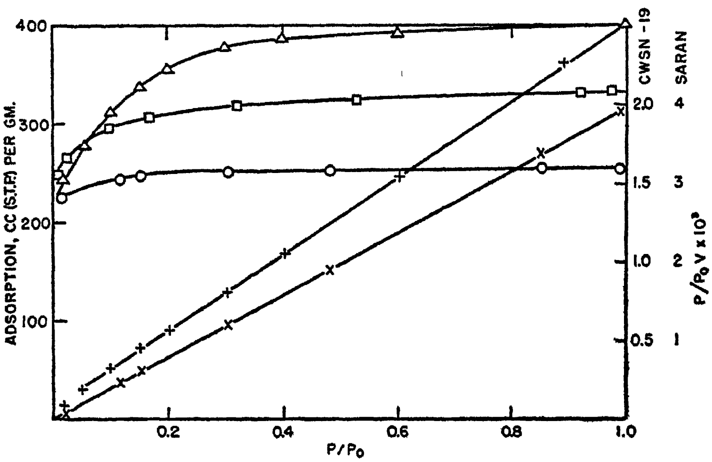


FIG. 5. Adsorption isotherms for nitrogen at −195°C.: △ CWSN 19; □, coconut charcoal; ○, Saran charcoal. Also, Langmuir plots (equation 4) of the data for Saran (×), and for CWSN 19 (+).

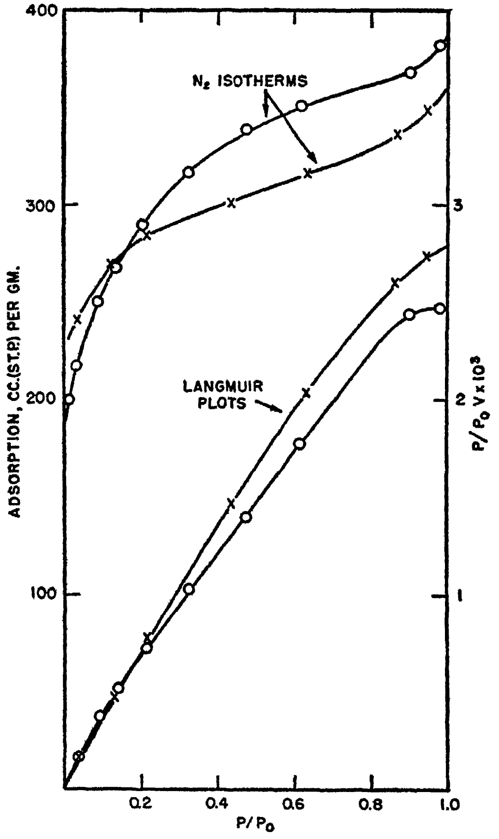


FIG. 6. Adsorption isotherms for nitrogen at −195°C. and Langmuir plots of the data for PCI P58 (×), and for a PCI special sample (○) that had been steam activated 350 min. during activation.

together as the activation proceeds, reaching area by nitrogen: area by butane ratios of 1.53 or 1.03, depending on which value is selected for the cross-sectional area of the butane molecule.

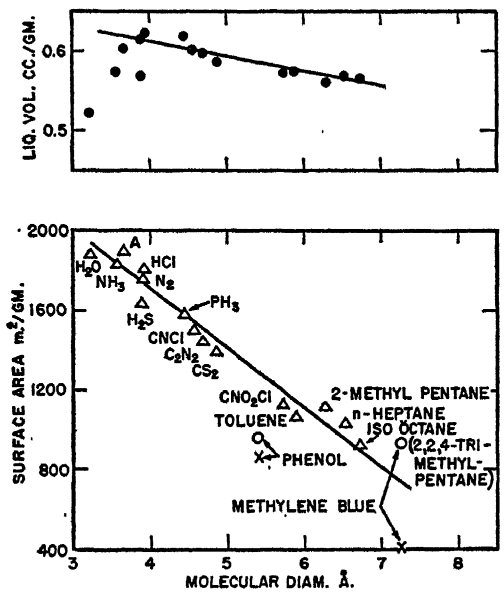


FIG. 7. Top curve is a plot of the adsorbate molecular diameter against the volume of adsorbate (calculated as liquid) taken up by CWSN 19 at $p/p_0 = 0.99$. The lower curve is a plot of surface areas (as calculated by equation 4) for the same adsorbates. The points indicated by open circles are from data by Young for the adsorption of phenol and methylene blue from solution onto crushed (100 mesh) charcoal samples; those marked X are for uncrushed samples for these same two adsorbates.

TABLE 2

Area of coconut shell charcoal (68) as measured by isotherms for nitrogen at 90.1°K. and n-butane at 0°C.

SAMPLE	ACTIVATION PERIOD	AREA IN SQUARE METERS PER GRAM			RATIO OF AREAS	
		By N_2 (17 Å.^{2})	By C_4H_{10}: (a) 32.1 Å.^{2}	By C_4H_{10}: (b) 48.0 Å.^{2}	$\frac{N_2}{C_4H_{10}(a)}$	$\frac{N_2}{C_4H_{10}(b)}$
	hours					
A..........	12	644	333	500	1.93	1.29
B..........	24	749	417	625	1.79	1.20
C..........	48	895	553	829	1.62	1.08
D..........	72	963	602	903	1.60	1.06
E..........	96	1070	703	1050	1.52	1.02
F..........	120	1136	737	1100	1.54	1.03

For obvious reasons it seems likely that the surface area measured by gas will be more important in judging the properties of charcoal than the areas measured by adsorbing molecules from a suitable liquid solvent. This is primarily due to the difficulty involved in causing a solute to diffuse through a solvent and cover the surface of capillaries when the latter are the order of a few molecular diameters in size. Nevertheless, some measurements of the surface area of charcoal by the adsorption of molecules from the solution have been made. In figure 7 a comparison is made between the area values obtained by phenol and methylene blue from solution and those obtained by adsorbing gas molecules of comparable size. The agreement on the crushed sample is fairly good; the areas on the uncrushed sample seem to be about 40 per cent lower by adsorption from liquid than by adsorption from gas. These few measurements from solution were not extensively or thoroughly studied. They are in sharp disagreement with the statement of Berl (23) that a good gas mask charcoal should adsorb only 25 mg. of methylene blue per gram of charcoal, corresponding to an area of only about 25 sq. m. per gram.[5]

TABLE 3

*Maximum millimoles of acids adsorbed, and surface areas in square meters, per gram of charcoal (104)**

CHARCOAL NO....	1	2	3	4	5	6	7	8
Acetic acid... ..	2.15	2.55	2.85	3.22	3.25	3.70	4.00	—† millimoles
	338	402	449	507	512	583	630	—† sq. m.
Propionic acid ..	1.63	2.04	2.47	2.91	2.93	3.46	3.75	3.96 millimoles
	257	321	389	458	462	545	590	624 sq. m.
Butyric acid. ...	1.24	1.66	2.06	2.63	2.74	3.43	3.84	4.25 millimoles
	195	262	324	415	432	540	605	670 sq. m.
Valeric acid... ..	0.88	1.31	1.75	2.40	2.41	3.18	3.66	4.01 millimoles
	139	203	276	378	380	501	577	632 sq. m.
Benzoic acid.....	0.89	1.26	1.71	2.25	2.31	2.91	3.38	3.70 millimoles
	140	198	269	354	364	458	533	583 sq. m.
Area by nitrogen adsorption‡.....	474	602	783	968	1045	1120	1330	— sq. m.

* Taken from Canadian Report dated September 20, 1943.

† Insufficient charcoal.

‡ The area values by nitrogen adsorption were furnished by Dr. J. H. Morrison by private correspondence. The author averaged two sets of values furnished by Dr. Morrison and recalculated the areas on the basis of 16.2 Å.^{2} per nitrogen molecule.

It is interesting to note that the areas obtained by Lemieux and Morrison (104), using acetic, propionic, butyric, valeric, and benzoic acids, all lie in the range 583–670 sq. m. per gram on a given sample of well-activated charcoal (table 3). As would be expected, the area measured by acetic acid was much larger for small degrees of activation than that measured by valeric acid, just as the area measured by chloropicrin or other large molecules is much smaller (65, 90) than that measured by nitrogen in the early stages of activation when, presumably, the smaller pores are predominant. It will be noted that the areas obtained by adsorption from solution are 30–70 per cent smaller than those calculated from the nitrogen-adsorption isotherm.

---

[5] It was assumed by Paneth that 1 mg. of methylene blue will cover an area of approximately 1 sq. m.

III. ADSORPTION OF WATER VAPOR

A. Adsorption isotherms for various charcoals and whetlerites

Hundreds of water-adsorption isotherms have been determined (59, 60, 65, 90, 154) in the course of the present work on a variety of charcoals and whetlerites and for a number of reasons. In the first place, the question arises as to the influence of water vapor on the chemical or catalytic activity of the whetlerites. Secondly, water is known (65, 109, 110) to be capable of inhibiting the adsorption of chloropicrin and other gases by charcoals, and hence can influence the life of a canister toward such gases. Finally, water-adsorption isotherms have proved to be of great value in estimating the pore size and pore-size distribution (68) according to a number of methods, including a new one developed by Juhola (90, 91, 92).

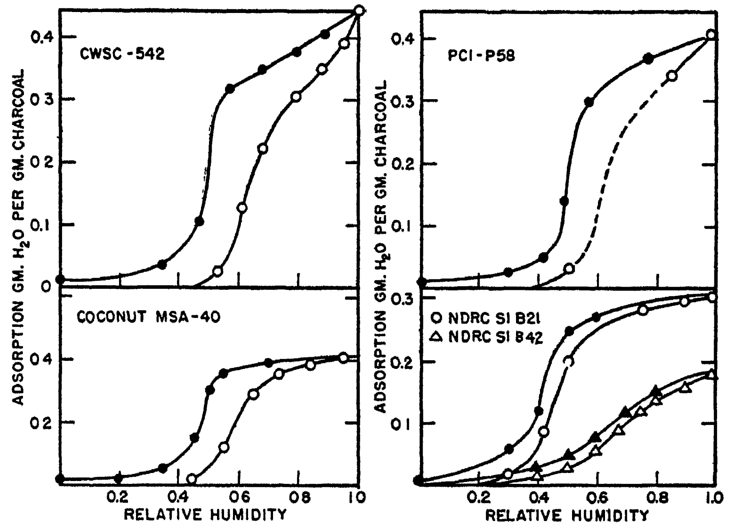


FIG. 8. Water-adsorption (open symbols) and water-desorption (solid symbols) isotherms for various charcoals at room temperature.

Various types of water isotherms (63) that have been found on charcoals by adsorbing and desorbing water vapor from a stream of air passing through the sample are illustrated in figure 8, and agree in general with those previously described in the literature (68, 96, 103). Most of the adsorptions are characterized by hysteresis that extends clear back to zero pressure when the isotherms are determined by a flow technique using air as a carrying gas. When the adsorption is measured by a static system after thorough evacuation of the sample, the shape of the hysteresis loop is somewhat altered and the desorption curve on at least some charcoals rejoins the adsorption curve at about 0.4 relative pressure

(65, 90), as illustrated in figure 9. However, Juhola has found (90) a number of examples of partially activated charcoals for which, even in a static system, hysteresis persists down to approximately zero relative pressure. In the author's opinion, any such hysteresis in physical adsorption extending to relative pressures below those corresponding to condensation on pores at least four molecular diameters in diameter is seriously to be questioned. Both slow chemical adsorption and gradual evolution of carbon monoxide or carbon dioxide from surface complex (13) or from ash in the presence of water vapor may be factors in apparent low-pressure hysteresis in water adsorption.

It has long been known that the shape of the adsorption isotherms for water vapor on a charcoal is radically influenced by the amount of oxygen present as a

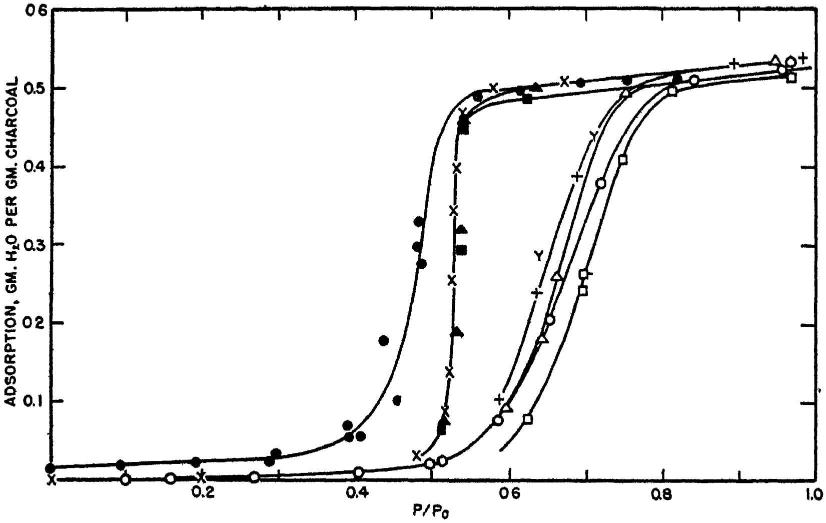


FIG. 9. Water-adsorption and water-desorption isotherms on CWSN 19 as determined by a flow system (○, ●) and by a static system. For the latter, samples were evacuated at 110°C. (+, ×, and Y for adsorption, desorption, and resorption, respectively); 500°C. (△ and ▲ for adsorption and desorption); and 900°C. (□, ■, □— for adsorption, desorption, and resorption).

surface complex. For example, it was pointed out by Lawson (103) and by King and Lawson (96) that the presence of an oxygen complex on the charcoal surface shifts the adsorption isotherm to lower pressures than those corresponding to the same adsorption in the absence of such a complex. The influence of oxygen coating a sample is illustrated by figure 10, in which the water-adsorption isotherm is shown for CWSN 19 both before and after exposing it to oxygen at 400°C. (60, 154). During this exposure the nitrogen isotherms remained practically unchanged.

The amount of water adsorbed has proved to be substantially independent (38) of the temperature between 15° and 40°C. at a given relative pressure for a number of charcoals (60, 154). This is not surprising since, for water, it is known that $E_1 - E_L$ in equation 2 is small. Consequently, the influence of temperature on the value of C and hence the amount of adsorption according to equation 3 is negligible over short temperature ranges, as illustrated (60) in figure 11 for water isotherms determined by a flow system for two different temperatures.

B. Rate of adsorption of water

The rate of adsorption of water vapor has received considerable attention because of the importance of knowing the rate at which canisters might be contaminated by picking up water vapor and the rate at which they could be dried out when necessary by sucking dry air through them. The following conclusions have been reached, although no complete mathematical analysis of the rates of adsorption and desorption has been reported (46a):

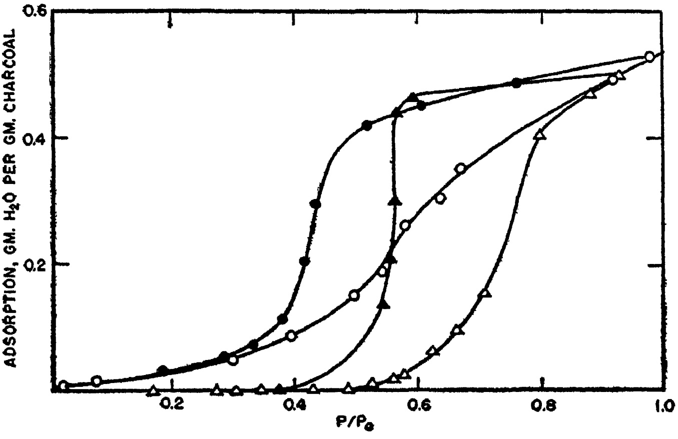


FIG. 10. Water isotherms on CWSN 19 before (△, ▲) and after (○, ●) surface oxidation. The oxidized sample (154) is CWSN 19 TUC 46.

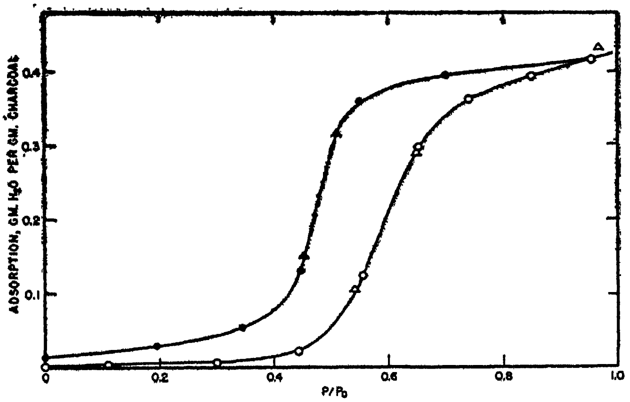


FIG. 11. Adsorption of water on Navy charcoal MSA Grade 40. Triangles are for 15°C.; circles, for 40°C. Flow system with air as carrying gas was employed.

(*1*) The rate of adsorption of water vapor by whetlerites is a little faster, and the rate of desorption somewhat slower than for the corresponding base chars (60). This is probably due to the fact that the equilibrium water-vapor curve is shifted toward lower relative pressures by whetlerization. Hence, for a gas stream of a given relative humidity the driving force for adsorption is greater than for the base char; similarly, the driving force for desorption into a dry gas stream is less for the whetlerites than for the base chars, and hence the rate of desorption is slower for the whetlerites than for the base chars.

(*2*) The rate of equilibration increases with the rate of gas passage (32, 33, 34) at a given relative humidity in the entering gas stream. This would be expected, because of the increase in the average partial pressure of water vapor throughout the charcoal column resulting from the higher gas velocity.

(*3*) Apparently (34) the slow step in the equilibration of charcoal with water vapor is not the mass transfer of the water vapor from the stream of gas to the charcoal particles, but the resistance encountered by the passage of the water vapor from outside the particle into the tiny capillaries. This has been pointed out by Colburn (34), who showed that the HTU (height of a transfer unit) for charcoal samples ranged from 3 to 25 in. under his experimental conditions compared to values of 0.2 to 1 in. for silica gel particles of similar size. This observation is consistent with the idea that some of the penetration of gases into the smallest capillaries is due to surface migration on the adsorbent (148). If the adsorption of water vapor is low, it would naturally follow that the transport of water vapor into the pores of the capillaries by surface migration and hence the rate of equilibration would be slow.

(*4*) At 30°C. and a gas flow of 600 cc. of air per minute per gram of charcoal, the time (60) for half-equilibration of several typical base chars ranged from 48 to 90 min.; the time for half-desorption into a stream of dry air at this same flow rate was about 30–40 per cent of the time of adsorption. The time required for the equilibration during the adsorption of water vapor on the whetlerites was from 30 to 60 per cent of the time required for equilibration of the base charcoals.

An analysis of the rate of adsorption of water vapor, carbon disulfide, and mixtures of these two gases has recently been published by Vreedenberg and van Nouhuys (146). According to the hypothesis of these authors, the rate of increase in the fraction, θ_1, of the surface covered by adsorbate is related to the relative pressure of water vapor, π, by the equation:

$$\frac{d\theta_1}{dt} = C\pi(1 - \theta_1) - D\theta_1(1 - \pi) \tag{7}$$

At the steady state at which $d\theta_1/dt = 0$, one then obtains an isotherm equation of the form:

$$\theta_1 = \frac{C\pi}{D + (C - D)\pi} \tag{8}$$

This contrasts with the rate equation that would be expected according to the Langmuir postulates:

$$\frac{d\theta_1}{dt} = C\pi(1 - \theta_1) - D\theta_1 \tag{9}$$

and the resulting isotherm equation:

$$\theta_1 = \frac{C\pi}{C\pi + D} \tag{10}$$

The logic behind equation 7 is not very impressive; it is argued that the desorption rate should be proportional not only to the fraction of the surface covered but to the distance between unity and the gas-phase relative pressure. Nevertheless, it must be admitted that equations 7 and 8 appear to fit the data of the authors (146) adequately, and even permit the calculation of the rate and equilibrium adsorption from mixtures. It is also true that equation 8 but not equation 10 can, by appropriate choice of constants, be made to represent the portion of the water-adsorption isotherm on charcoal that is convex to the pressure axis.

C. Nature of water adsorption on charcoal and whetlerites

Much has been written (38, 112, 121) relative to the nature of water adsorbed on charcoal. This is understandable, since the interpretation of the water isotherms may be a key to the calculation of the pore size and pore-size distribution of the adsorbent. If water is adsorbed in or desorbed from a state that may be called capillary condensation, then the adsorption or desorption curves may be used with the help of an appropriate equation such, possibly, as that of Kelvin to estimate the pore-size distribution. In the next section we shall see how this method has actually been applied by Juhola and others. For the present we shall limit our discussion to a presentation of the evidence that has been accumulated as to the nature of water adsorption. In particular, the evidence will be summarized on the question of whether water pickup by charcoal is adsorption, capillary condensation, or a combination of both.

McBain (120, 121) and his coworkers have contended that the sorption of water vapor by charcoal is an adsorption phenomenon and is not capillary condensation. In favor of this point of view are the following experimental facts:

(*1*) When water vapor is taken up by charcoal the latter expands (121) rather than contracts.[6] It seems agreed that pure capillary condensation would lead to a tension in the pores of the charcoal and hence to a slight contraction.

---

[6] Very recent publications throw doubt on this conclusion of McBain, Porter, and Sessions (121). Haines and McIntosh (121a) have found that a carbon rod made up of active charcoal (made by the zinc chloride process) contracts during the desorption of water as the relative humidity is lowered, but at 75 per cent relative humidity reaches its normal length, and at 50 per cent relative humidity is shorter than the original rod by 75 microns (about 0.08 per cent). At still lower relative humidities as the major portion of the desorption occurs, the charcoal *expands* back to its original length as water is *removed.* Wiig and Juhola (121b) have found that a stack of activated charcoal blocks behaves on both adsorption and desorption as the rods of Haines and McIntosh behaved on desorption. These latter authors failed to detect any length change on adsorption until a relative humidity of about 70 per cent was reached. Between 70 and 96 per cent Haines and McIntosh found a linear expansion of the rod with relative humidity, the final value (~0.1 per cent) at 90 per cent for 20°C. being in good agreement with the final value of McBain, Porter, and Sessions, 0.13 per cent at 27°C. at about 100 per cent relative humidity. Both

(2) McBain, Porter, and Sessions (121) succeeded in drying and evacuating a sugar charcoal sufficiently to eliminate all hysteresis in an isotherm at 120°C. The results of their measurements are shown in figure 12. They are very similar in many respects to some of the "first-order" phase transitions observed by Harkins and Jura (77) and his coworkers for various gas–solid systems. The water sorption rises abruptly at a relative pressure of about 0.3 until about 80 per cent of the sorption capacity of the charcoal is satisfied. It then levels off gradually to a constant saturation value. Desorption follows the same curve. On the other hand, after the charcoal had stood in contact with the water vapor for a year with the development of detectable amounts of hydrogen, a repeat adsorption run at 120°C. showed the conventional type of adsorption (curve 2, figure 12) with hysteresis in desorption; the adsorption and desorption curves at

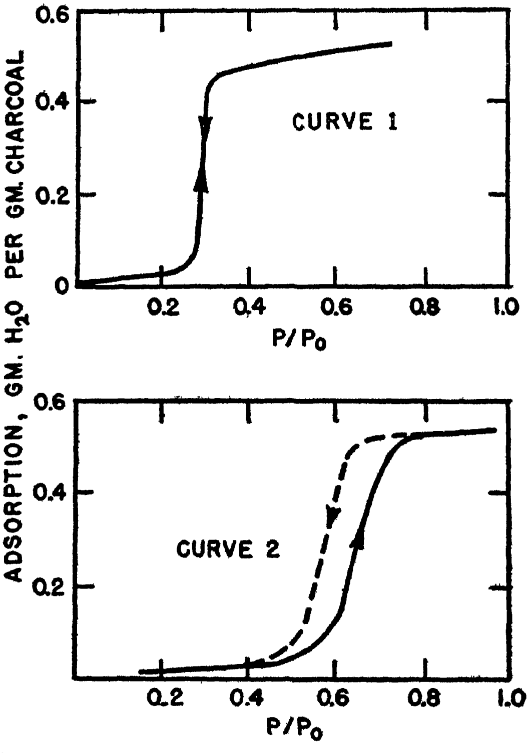


FIG. 12. Water adsorption on charcoal (121) at 120°C. Curve 1 is for a highly degassed and dried sample of sugar charcoal; curve 2 is for the same sample after continuous exposure to water vapor for 15 months.

---

of the recent papers would, therefore, seem to agree that the escape of water from charcoals in the relative pressure range in which most of the desorption occurs (as in the almost vertical section of the desorption curve of the highly degassed charcoal, as shown in figure 9) is from water that seems to be held by capillary condensation.

60°C. on this sample both agreed approximately with the desorption part of curve 2 of figure 12.

(3) The shapes of the lower parts of the water isotherms such as shown in figures 8 and 9 are not very different from the shapes of the water isotherms obtained by Emmett and Anderson (54) on samples of degassed carbon black (figure 13) or by Harkins, Jura, and Loeser (78) on graphite. It will be noted that the nitrogen isotherms on the carbon black before and after evacuation at 1000°C. are practically identical. On the other hand, the water-adsorption isotherms are greatly changed. The sample after the high-temperature evacuation adsorbs no water at low relative pressures but picks up increasing amounts as the relative pressure is increased. The isotherms apparently indicate a heat of adsorption that is smaller than the heat of liquefaction. The water isotherm before evacuation rises almost linearly with relative pressure in much the way one would expect if the heat of adsorption is substantially equal to the heat of liquefaction. It seems clear that on the degassed carbon black the water adsorption cannot be due to capillary condensation, since there is no evidence of any capillaries being present. Certainly, the high-temperature evacuation did not produce capillaries, or the nitrogen-adsorption isotherms would have been quite different before and after the evacuation. The similarity between the shapes of the two carbon black water-adsorption isotherms and the shapes of the isotherms of water vapor on charcoals is striking; one must accordingly certainly be cautious about interpreting the water-adsorption isotherms on charcoal as due to capillary condensation.

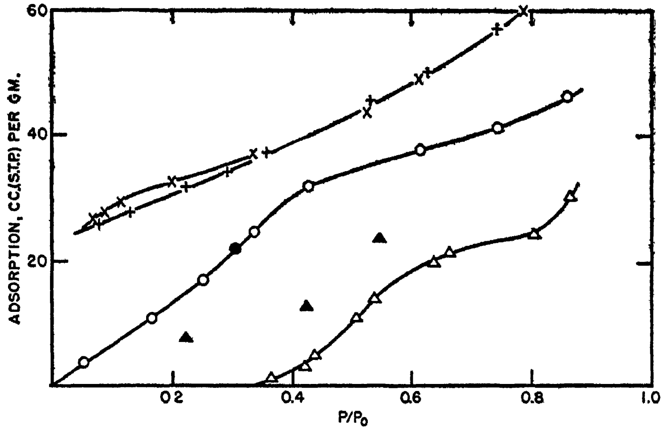


FIG. 13. Adsorption of nitrogen at −195°C. and water vapor at 25°C. on Grade 6 carbon black (54). ×, nitrogen before degassing at 1000°C.; +, nitrogen after degassing. Circles are for water isotherms before degassing at 1000°C.; triangles are for sample after degassing. Solid circles or triangles are for desorption points.

The evidence for interpreting the isotherms as an indication of water being held on the charcoal by capillary condensation is also strong:

(*1*) No satisfactory explanation of hysteresis in desorption has so far been advanced for any process other than capillary condensation. A recent paper by Gleysteen and Deitz (72) suggested that if one applies the multilayer theory of Brunauer, Emmett, and Teller to the adsorption isotherms at high relative pressures in place of the capillary condensation theory and then assumes that desorption involves a larger heat than adsorption, hysteresis can be accounted for. It remains to be explained why the heat of desorption should be larger than the heat of adsorption. However, in the water isotherms on the degassed carbon black (54) in figure 13, hysteresis appears to exist. If these observations are confirmed by further work they will tend to undermine the capillary condensation interpretation of hysteresis, since the particle size in the carbon black work is such that even capillary condensation between the particles seems to be ruled out.

(*2*) By assuming that the shape of the adsorption isotherms of water vapor on charcoal is due to capillary condensation and that $\cos \theta$ in the Kelvin equation

$$\ln p/p_0 = -\frac{2\sigma V \cos \theta}{rRT} \tag{11}$$

has a value of 0.5–0.6, Juhola has been able to calculate pore-size distributions for charcoals that yield good values for the surface areas measured by nitrogen adsorption. This work will be considered in detail in the next section.

(*3*) In the writer's opinion, the most convincing evidence that even the adsorption curve is partly capillary condensation has been obtained by Juhola in his scanning runs (90). A typical set of these is shown in figure 14. Unless some explanation for hysteresis based purely on adsorption is forthcoming, these scanning runs must be considered definite evidence that a part at least of the adsorption isotherm for water on charcoal is due to capillary condensation.

Perhaps the soundest interpretation of water isotherms at the present time is that they are some combination of adsorption and capillary condensation. In water isotherms such as shown in figure 14, it seems reasonable to assume that on the adsorption part of the curve the adsorption increases with relative pressure, passes through a maximum, and then decreases as more and more of the surface is eliminated as a result of the capillaries filling with condensed water. At high relative pressure near saturation (107) this interpretation would say that most of the water pickup is due to capillary condensation (26). It should be noted, however, that if this picture is adopted and if the same angle of wetting, density, and surface tension characterizes the condensed liquid during both adsorption and desorption, then one must conclude that the capillary condensation on the adsorption part of the curve does not occur at the relative pressures indicated by the Kelvin equation. For some reason that is not as yet certain it would appear that capillaries of a particular size fill with condensation only at relative pressures that are considerably higher on the adsorption side of the curve than on the desorption branch. Perhaps the bottleneck theory of Kraemer (98) or the "open pore" theory of Cohan (37) can supply the explanation for the hysteresis. Indeed, Fineman, Guest, and McIntosh (68) conclude that Cohan's open-end pore theory yields good values for the size of capillaries in several charcoals with which they worked.

Some idea as to the nature of water in capillaries might normally be expected from measurements of freezing points and measurement of the density of the water sorbed by the charcoal. Two sets of measurements of the density of the water in the charcoal have been made. They disagree sharply with each other. Morrison and McIntosh (123) obtained values ranging from 1.01 to 1.16, 0.95 to 1.04, 0.99 to 1.15, and 0.98 to 1.17 for four charcoals exposed to relative humidities below 100 per cent. On the other hand, three runs with pure water at 100 per cent relative humidity resulted in the sorbed water having apparent densities of 0.95, 0.94, and 0.93. In contrast to this Wiig and Juhola (151) have found consistently that on activated charcoals the apparent density of water is less than unity, over the entire range of relative humidities, values of approximately 0.93 and 0.90 characterizing adsorption and desorption parts of a run. It is

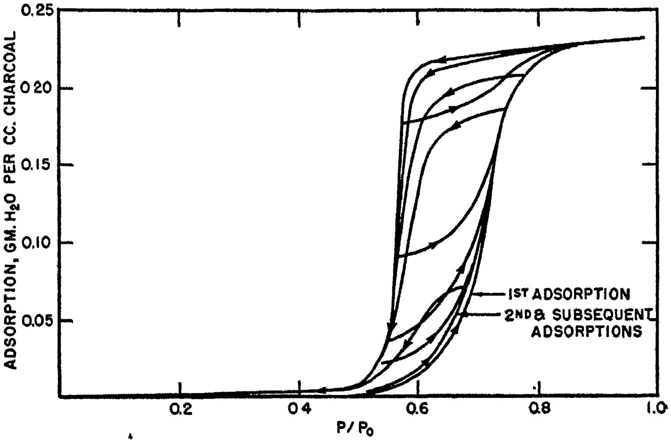


FIG. 14. Water-adsorption isotherm on CWSN 291 AY1 (90); scanning curves are also shown

difficult to be sure of the cause of this discrepancy. The writer would be a little suspicious of the procedure used by the Canadian workers for getting relative humidity values smaller than 100 per cent. The use of sulfuric acid to decrease the partial pressure of water vapor in their experiments might have contaminated the charcoals with small amounts of acid spray or sulfur trioxide. Either of these would have a much higher density than water and would cause the apparent density values to be erroneously larger. In agreement with this, it should be noted that the values obtained by Morrison and McIntosh (123) using pure water (100 per cent relative humidity) for saturating the sample are in satisfactory agreement with Juhola's results.

Another possible source of error in the results of Morrison and McIntosh (123) has been suggested by Wiig (149). In the course of their measurements, they expanded a helium–water vapor mixture containing p mm. of water vapor into an adsorption bulb containing charcoal equilibrated with water vapor at p mm. Wiig points out that such a procedure causes the pressure of water vapor in the charcoal bulb to be greater than p, and in the helium buret less than p. Unless the 18–24 hr. equilibration time is sufficiently long to permit a reëstablishment of the partial pressure of water vapor to p mm. throughout the system, the apparent density values will be high. Because of the fact that the blocking of submicropores by capillary condensation of water or the fact that water is under tension in capillary condensation would both tend to make the density less than 1, it seems likely that the values obtained by Juhola for the apparent density of water are more nearly correct than the high density values obtained by McIntosh and Morrison.

Freezing methods have also failed (27) to help much in revealing the nature of adsorbed water. Johnstone and Clark (85) found that charcoals such as CWSN 19 when equilibrated with water sufficient to cause a 45 per cent weight increase on a dry basis (probably equilibrated at about 75 per cent relative humidity) failed to yield an ice pattern at −30°C. On the other hand, a sample soaked in water initially and then air dried to a damp powder showed ice crystals that were much smaller than those obtained by allowing moisture from the air to condense on the cold cassette. It seems likely that the water picked up during adsorption at 75 per cent relative humidity is either held by adsorption as a monolayer or else is in the form of capillary condensation in capillaries as small as 20 Å. in diameter. It is, therefore, understandable why the sample equilibrated at 75 per cent relative humidity failed to show an x-ray pattern. The pattern shown by the sample initially exposed to liquid water vapor and retaining about 75 per cent water by weight could easily be due to a thin film of water located in the larger capillaries of the charcoal or adhering to the outer periphery of the particles. A 75 per cent weight increase is considerably higher than one would expect from adsorbed water on CWSN 19 even at saturation. Accordingly, this observation does not reveal the nature of the water that is contained in the capillaries in normal water adsorption up to, say, 99 per cent relative humidity.

Culbertson and Winter (41) have shown that a considerable amount of water taken up by charcoal does not freeze until the temperature is well below 0°C. Even at −40°C. some of the water apparently remains unfrozen. However, as they point out, absence of good heat-capacity data (39) for adsorbed water prevents exact calculation as to the amount of water in a "bound" state on the charcoal surface.

Another approach toward throwing some light on the question of the nature of adsorbed water was made by comparing the nitrogen adsorption on dry charcoal with that on samples that had been partially equilibrated with water vapor. Such measurements (65) showed that on both PCI P58 and CWSN 19 charcoals there is no sudden expansion of water as the temperature is dropped until some point between −78° and −195°C. is reached. This seems to point to the conclusion that the water held by the two above-mentioned charcoals at 83.5 and 96 per cent relative humidities, respectively, is not water having a normal freezing point. However, much further work would be required before one could be sure of the influence of the size of a capillary on the freezing point of liquid contained in it. Hence even this observation is a bit indefinite as an indication of the nature of the water held in capillaries.

IV. PORE SIZE AND PORE-SIZE DISTRIBUTION

No entirely satisfactory method has been discovered for measuring pore size and pore-size distribution in charcoal and other similar small-pore materials. The difficulties encountered are many. Perhaps one of the principal complications has to do with the shape of the capillaries. Not only is it impossible to ascertain whether the capillaries are cylinders, cracks with parallel walls, crevices, cones, or other regular geometric shapes, but it is impossible to tell what combination of all of these and other irregular forms may be involved. Furthermore, it must be realized that in dealing with capillaries that are one to ten molecular diameters in size, one has little information as to the way in which density, surface tension, and other properties of the adsorbed molcules may differ from those of the adsorbate in bulk form. It would probably, therefore, be difficult to specify "pore size" even if we knew the exact shape of all capillaries present. Accordingly, progress in estimating pore diameters of charcoal is possible only by virtue of making assumptions as to the shapes of the capillaries and the properties of the adsorbed molecule. It is gratifying that, in spite of the numerous assumptions and approximations that had to be made, methods were worked out during the recent war that are certainly more satisfactory than any previously available and that give results that are useful in trying to approach the ideal type of adsorbent for gas mask work.

Methods for measuring pore size that have been employed on the charcoal work may be listed in the following five classifications: (*1*) Study of adsorption as a function of the size of the adsorbate molecules (65). (*2*) Application of the Kelvin equation to the adsorption and desorption of any gaseous adsorbate other than water vapor (65). (*3*) Application of the Kelvin equation to the adsorption (68, 112) and desorption (90) isotherms of water vapor. (*4*) Measurement of the change of surface area resulting from the pickup of water by the charcoal (90, 91, 92). (*5*) Measurement of the pressure required to force mercury (51, 59, 90, 147) into the charcoal capillaries. These five methods will now be considered in turn.

A. Molecular size as a criterion of pore size

In a general way it would seem to be possible to tell a great deal about the size of pores in charcoal by comparing the change in the amount of adsorption with the size of the adsorbate molecule. For example, experimental work on chabazite has shown rather clearly that it is possible so to prepare the adsorbent (18, 19, 57, 101, 138) as to make the pores capable of adsorbing molecules of a given adsorbate and yet screening out almost completely molecules of only a slightly larger size. Thus, as a function of the temperature and time of dehydration, as pointed out in an earlier section, chabazite can be made to adsorb hydrogen but not nitrogen, oxygen but not nitrogen, nitrogen but not butane, and normal hydrocarbons but not branched-chain hydrocarbons. However, this apparently simple method becomes very complicated if the adsorbent is one in which only a partial screening out of the larger molecules occurs. One is then faced with the task of differentiating between screening effects and the influence of the tightness of packing of odd-shaped molecules in capillaries of unknown shape. For example, it is known that if one compares the surface area of CWSN 19 obtained by the adsorption of nitrogen with that obtained by use of successively larger molecules, one obtains (figure 7) a decrease of about 50 per cent in going to isoöctane (65). It is not at all certain, however, that this means that one-half the area is located in pores intermediate in size between that of the nitrogen molecule (about 3.9 Å.) and that of the isoöctane molecule (about 6.7 Å.). Much of the decrease may be attributed to the less efficient packing of large molecules onto a given area than the corresponding packing of smaller, more symmetrical molecules. Indeed, it is not even well established as yet that, for nonporous adsorbents, the same areas can be obtained by using large molecules as measuring units as by using smaller ones (20, 53). In spite of this, adsorbates whose molecules are of different sizes have been used effectively for at least qualitative appraisal of the relative pore sizes of two different charcoals. For example, it is claimed in the literature (103, 120) that large dye molecules are almost completely excluded from the pores of many charcoals. As a matter of fact, decolorizing carbons for removing color from sugar solutions commercially are known to have much larger pores than the charcoals or activated carbons intended to adsorb large quantities of gas. Furthermore, some unmistakable screening effects can be noticed for molecules differing as little in size as nitrogen and isoöctane. For example, charcoals made from carbonization of certain plastics are known to have uniformly small pores. Thus, Saran charcoals will adsorb up to twelve times (65) as many molecules of nitrogen as of isoöctane and will equilibrate very much faster with nitrogen than with isoöctane. It seems likely that most of the pores of this material are in the range 5–10 Å. in diameter. Again, it has been found that charcoals made by the activation of coal develop pores capable of adsorbing nitrogen much earlier than they develop pores capable of adsorbing molecules as large as chloropicrin or isoöctane. Accordingly, in a qualitative sense, at least, the relative amounts of adsorbate picked up as a function of the size of the adsorbate molecule can be used to obtain some idea as to the distribution of pore sizes in charcoal.

Attention should, perhaps, be called to one other precaution in judging the size of capillaries by the size of the adsorbate molecules. If one compares the amount of adsorption in terms of the volume of adsorbate (calculated as normal liquid) picked up, he occasionally obtains some odd results. For example, on two samples of charcoals on which the pores had been partially plugged by the product from the oxidation of arsine, the volume of liquid isoöctane adsorbed near saturation was greater (66) than the volume of nitrogen (as liquid) adsorbed near saturation. Specifically, the ratios of the volumes of isoöctane to nitrogen were 1.3 and 1.6, respectively, for the two samples. This can be understood if one remembers that, if two plane parallel walls were completely covered with adsorbate molecules and were exactly 12 Å. apart, then the volume of liquid calculated for an adsorbate that had molecules 6 Å. in size would be nearly 50 per cent greater than that of an adsorbate that had molecules 4.2 Å. in size. Such extreme cases are rarely encountered, though it is observed that the liquid volume of adsorbates of successively larger size picked up by a charcoal do not fall off (figure 7) as rapidly as do the apparent surface areas as calculated from the molecular cross section. This may result from the effect of the thickness of the adsorbed molecule entering into a calculation of the volume of liquid picked up when much of the adsorption is necessarily only a single layer in thickness.

The adsorption of dyes by activated carbons and charcoals is being extensively and thoroughly studied by Deitz and his coworkers at the Bureau of Standards. Adsorption of dye and other organic molecules is being compared with the low-temperature adsorption of nitrogen. Deitz has already made it clear that such measurements are fraught with many difficulties that have not usually been taken into consideration. His work when completed should give a final answer to the extent to which adsorption of big molecules from solution may be considered as significant in pore-size determination.

B. Pore size by applying the Kelvin equation to the adsorbates other than water

A general method for measuring the diameter (D) of pores that has often been suggested makes use of the Kelvin equation,

$$D = -\frac{4\sigma V \cos\theta}{RT\, 2.303 \log p/p_0} \tag{12}$$

where V is the molal volume, σ is the surface tension, T is the temperature at which the adsorption is measured, and p/p_0 is the relative pressure of the adsorption. θ is the angle of wetting of the walls of the capillaries by the adsorbate. The equation in this form assumes that the capillaries are circular in cross section.

Two serious complications arise from trying to use this method in practice. For substances having large enough pores to give smooth S-shaped curves of the type shown in figure 1, it becomes very difficult to differentiate between an increase in adsorption due to capillary condensation and one due to multimolecular adsorption. Indeed, some (28) interpret the upper part of the adsorption isotherms of curves such as shown in figure 1 for carbon and also those shown in figure 15 for porous glass as due entirely to multilayer adsorption rather than to capillary condensation. Wheeler (21), Ritter (133), and Shull (139) are having some success in separating the multilayer adsorption effect from the capillary condensation effect and thereby are able to obtain fairly satisfactory pore distributions from nitrogen-adsorption isotherms on gels at −195°C. For the most part, however, this confusion between multilayer adsorption and capillary condensation effects has not been satisfactorily resolved and hence makes it difficult to use equations in conjunction with non-aqueous adsorbates in calculating pore diameters of charcoal.

A second difficulty encountered in attempting to calculate pore diameters by use of the Kelvin equation has been pointed out in the literature (11, 57, 70) on a number of occasions and is especially applicable to fine-pore solids such as charcoal. It has to do with the question of whether the diameter mentioned in the Kelvin equation (equation 12) is the diameter of the capillary *after* a monolayer has been adsorbed or before it has been adsorbed. If the capillaries are large enough to permit multilayer adsorption, the thickness of the layer left on the surface after a capillary empties at some given desorption pressure also comes into consideration, since, according to the multilayer theory (29), one may have several statistical layers left on the surface at sufficiently high relative pressures. This second difficulty can perhaps best be discussed in connection with figure 16, showing the adsorption and desorption isotherms for nitrogen on several typical charcoals. It will be noted that the desorption isotherms show some hysteresis compared to the adsorption isotherms. The desorption curve, however, rejoins the adsorption curve at about 0.35–0.4 relative pressure.

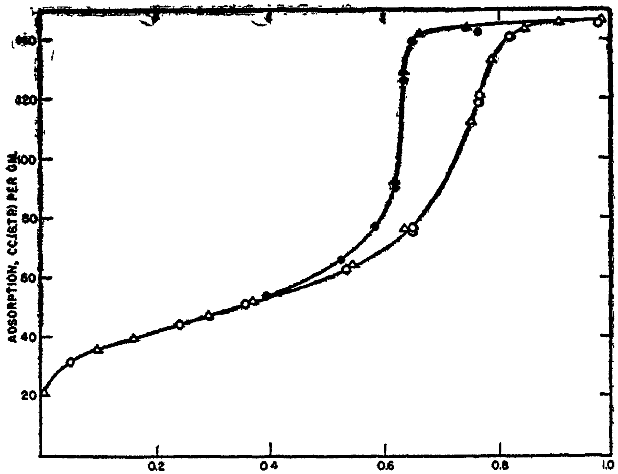


FIG. 15. Adsorption of nitrogen on porous glass at −195°C.; solid symbols are for desorption

It has been pointed out by Cohan (37) that for a large number of adsorbates the desorption isotherms rejoin the adsorption isotherms at a relative pressure which, according to the Kelvin equation, calculates out to correspond to four molecular diameters. On such a basis the adsorption of nitrogen on the charcoals shown in figure 5 would indicate only a comparatively small pore volume in the pore diameter range between 20 Å. and about 2000 Å. (this latter value being the upper limit fixed by the highest relative pressure—0.99—to which the runs were carried). For charcoals such as those shown in figure 16, on the other hand, definite qualitative evidence is given by the nitrogen isotherms as to the presence of capillaries in the range 20–2000 Å. in diameter.

The two complications discussed thus far are involved even when the desorption curve shows marked hysteresis in comparison to the volume of gas picked up at a given relative pressure during adsorption. Matters are made even more complicated by the fact that, according to some interpretations of capillary condensation, one may not obtain any hysteresis (37) even though capillary condensation is occurring. It is claimed, for example, that if capillaries are wedge-shaped no hysteresis is to be expected. Also, if they are cylindrical but have some narrow portion less than four molecular diameters in diameter they will not, according to certain hypotheses (37), give hysteresis. For all of these various reasons it may be concluded that deductions as to capillary size and distribution based on the adsorption of molecules other than water vapor are susceptible to only qualitative interpretations at best. Even if hysteresis (the usually accepted criterion for capillary condensation) occurs, the interpretation of the results on a quantitative basis is made very difficult if not impossible by the uncertainty as to the thickness of the adsorbed layer left after evaporation of the portion of the sorption that is due to capillary condensation.

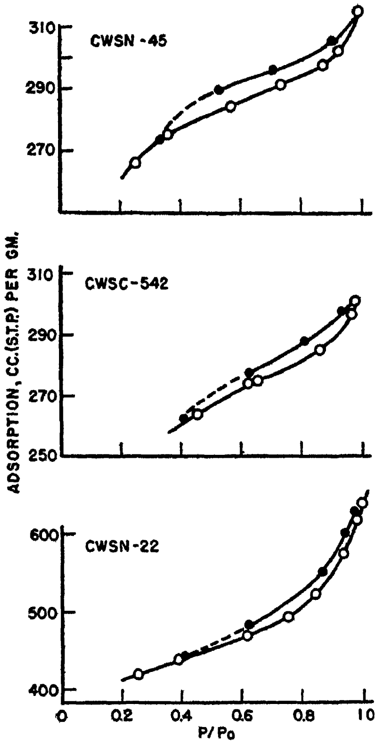


FIG. 16. Nitrogen adsorption and desorption isotherms at −195°C. on several different charcoals.

There is one adsorption region in which the Kelvin equation may be applied to nitrogen isotherms with a somewhat greater assurance than indicated above. It is the range near saturation extending up to the highest relative pressures that can be conveniently measured. By the use of the Pearson gauge (59) for measuring pressures very close to saturation, nitrogen-adsorption measurements have been made on several charcoals. Typical adsorption data (59a) are plotted in figures 17 and 18. The adsorption in the range 0.99–0.999 covers diameters between 1800 and 18,000 Å., if one assumes that the Kelvin equation is valid for the calculation. The question may well be asked as to whether the abrupt rise in some of the isotherms in this relative pressure range may not be partially due to the formation of multilayers on the surface of the large pores. It is difficult to give an exact answer in the absence of any certain knowledge as

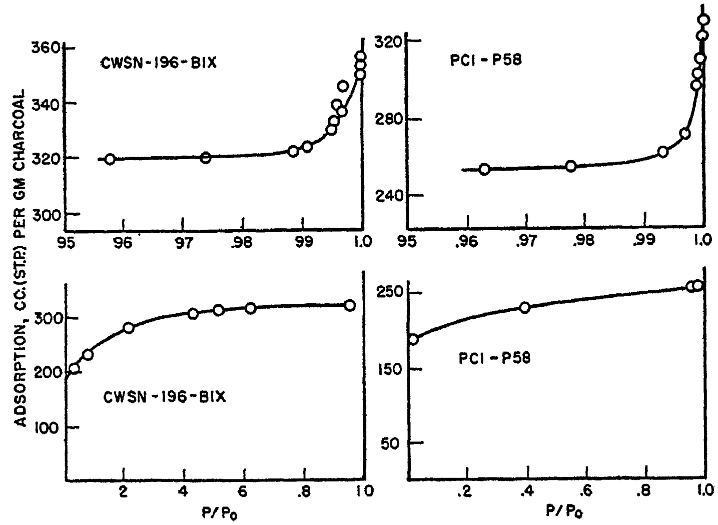


FIG. 17. Adsorption of nitrogen at −195°C. up to high relative pressure (0.999) on two different charcoals.

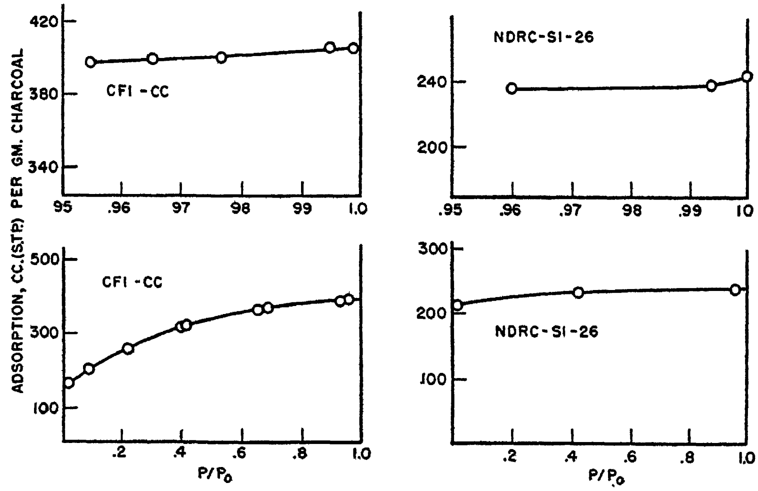


FIG. 18. Adsorption of nitrogen at −195°C. up to high relative pressure (0.999) on charcoals CFI "CC" and NDRC SI 26.

to the thickness of films that will be built up without capillary condensation. The B.E.T. equation (29) if followed would predict layers 1000 molecular diameters in thickness at a relative pressure of 0.999 and a C value of 100. However, this is certainly much on the high side, since the B.E.T. equation predicts adsorption that is too high at all relative pressures above 0.35. It seems more likely from the few measurements reported in the literature (37) that no more than 50 layers would be built up. This would mean that the multilayer built up would be no more than about 10 per cent of the total volume of liquid required to fill pores of this size and hence could be neglected. As shown in figure 18, both Saran and CFI "CC" charcoals show no adsorption increase between 0.99 and 0.999; on the other hand, the charcoals shown in figure 17 have a considerable increase in adsorption in this range of relative pressure.

Perhaps it would be more nearly correct to interpret adsorption isotherms at high relative pressures as leading to minimum values for the volume of pores in the size range covered by the isotherms. This precaution is suggested by the experiments of Bangham and Razouk (16), who claim that the large pores (200,000 Å.) of a charcoal with which they were working would not fill up even when p/p_0 was increased to 1. Only immersion of the samples in the liquid adsorbate caused these large pores to fill up.

It has been pointed out that by selecting proper adsorbates having large products of $V\sigma/T$ (see equation 12) it is possible to extend the pore measurements to larger diameters without working at higher relative pressures. Carbon tetrachloride (125), pyridine (126), and tributyrin (127) have been employed in this way to extend the measurements to 4000, 5000, and 13,500 Å., respectively.

C. Pore size from water adsorption and desorption isotherms

It has been suggested (68, 112) that adsorption isotherms for water vapor on charcoals can be used for calculating pore-size distributions. However, there seems good reason to doubt that all of the water picked up by charcoal during adsorption is held by capillary condensation. The similarity between the adsorption isotherms for water vapor on well-degassed, non-porous carbon black (54) and those for charcoals such as shown in figures 9, 10, 11, 12, and 14 suggests caution in making any pore-size calculations from the adsorption curves. On the other hand, the desorption isotherms for some of the charcoals give every indication of representing the emptying of capillaries with little or no residual adsorption. Therefore, calculations such as those of Juhola, described below, seem entirely warranted provided the charcoals used are those having negligible adsorption below about 0.4 relative pressure.

If one applies the Kelvin equation to a desorption isotherm such as shown in figure 14, and uses a value of unity for cos θ, one obtains pore diameters in the range 30–40 Å. for most of the sample. These clearly are too large, for they would not afford a sufficiently large area for the observed pore volume to account for the surface area measured by nitrogen adsorption or by the adsorption of other gases. There seem to be two alternatives in interpreting the desorption curves. The possibility exists that the angle of wetting is not zero degrees but an angle of such size as to yield a cos θ between 0.5 and 0.6. As will be seen in the next section, such a choice of cos θ yields pore-distribution curves that appear to be very reasonable. On the other hand, one might be inclined to interpret the result to mean that cos θ is equal to 1, but that attached to each of the 30–40 Å. pores are a number of smaller pores in the range 10–20 Å. diameter which adsorb water only when the larger pores are filled. An obvious weakness in this latter interpretation is that it does not account for the absence of an appreciable number of pores in the range 20–30 Å., in which it is generally believed that capillary condensation can occur.

It must be kept in mind that it is entirely within the realm of probabilities that the value of cos θ changes as a function of the relative pressure. As a matter of fact, the heat of adsorption would be expected to increase to a value corresponding to the heat of liquefaction of water vapor as soon as the surface is covered with a monolayer of adsorbed water vapor. From experiments on carbon black (54) that has been stripped of its surface complex by high-temperature evacuation, it appears that a monolayer of adsorbed water formed at about 0.85 relative pressure. It might not be surprising, therefore, by analogy to expect the cos θ term to become substantially unity above 0.8–0.9 relative pressure. Furthermore, the shift (154) of the steep part of the desorption part of a water isotherm to lower relative pressures as one coats the surface with chemisorbed oxygen is an indication that cos θ for a complex-covered surface is greater than for one without a surface coating.

D. Pore size from changes in surface area resulting from water uptake by charcoal

It is well known that for cylinders the diameter, D, the volume, V, and the area, A, are related by the equation:

$$D = \frac{4V}{A} \tag{13}$$

Similarly, if one pictures charcoal as a collection of cylindrical capillaries and imagines that a group of capillaries of a particular size are filled by capillary condensation, then the small change in available volume in the charcoal will be related to the diameter of the capillary and the change in available area by the equation:

$$D = \frac{4\Delta V}{\Delta A} \tag{14}$$

Juhola and Blacet (91) were the first to point out that by measuring the surface area of a charcoal with nitrogen at liquid nitrogen temperature as a function of the amount of water present, one could obtain a curve from which the pore-diameter distribution of the charcoal could be calculated. The water-desorption isotherms for the charcoals used are shown in figure 19. The changes in area *vs.* volume curves are shown in figure 20, and the resulting plots of pore diameters against relative pressure of condensation of water are shown in figure 21. It soon became apparent that the technique of measuring pore diameters by this procedure would be quite laborious. Juhola, therefore, suggested using the method merely as a means of evaluating the cos θ term of equation 12 and thereafter using this latter equation for pore-size measurements in conjunction with water-desorption data. He has used this method extensively (90) for obtaining pore-size distribution over the diameter range up to about 100 Å.

Juhola states (90) that the Kelvin equation with cos θ equal to about 0.53 agrees satisfactorily with the curves obtained by use of equation 14 applied to the surface area *vs.* volume experiments at relative pressures up to about 0.9, but not above this relative pressure. Actually, there is less reason to expect the

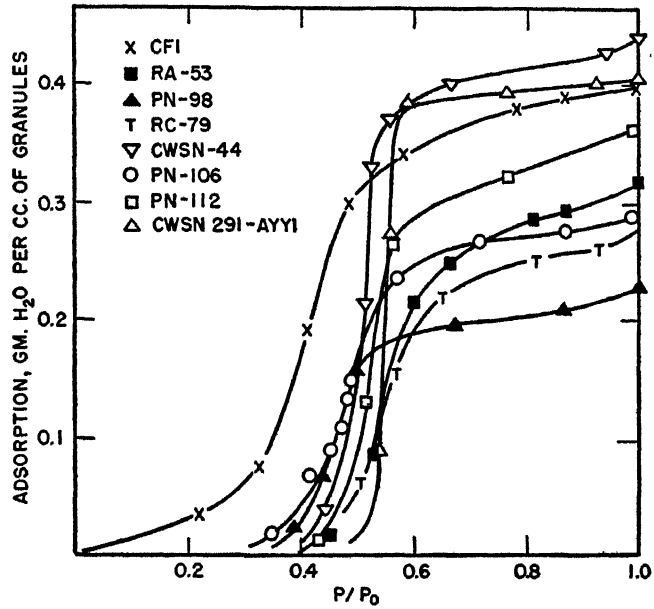


FIG. 19. Water-desorption isotherms for a series of charcoals (91)

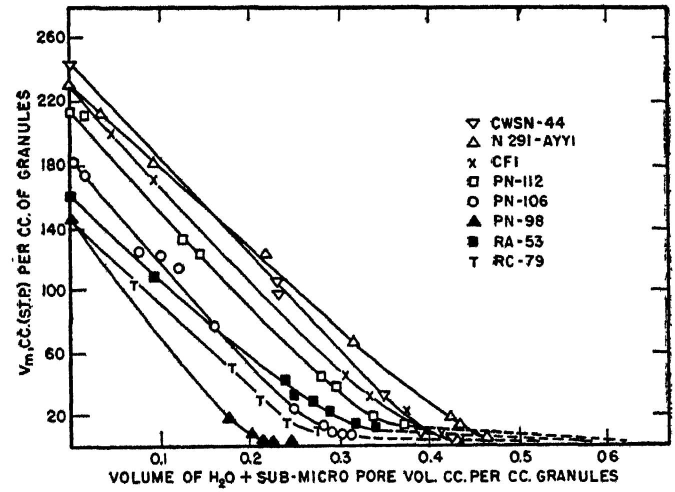


FIG. 20. V_m values for the residual surface of charcoals left after the adsorption of various amounts of water.

Kelvin equation to fail at relative pressures above 0.9 than at lower relative pressures. From comparison with the water-adsorption experiments on de-

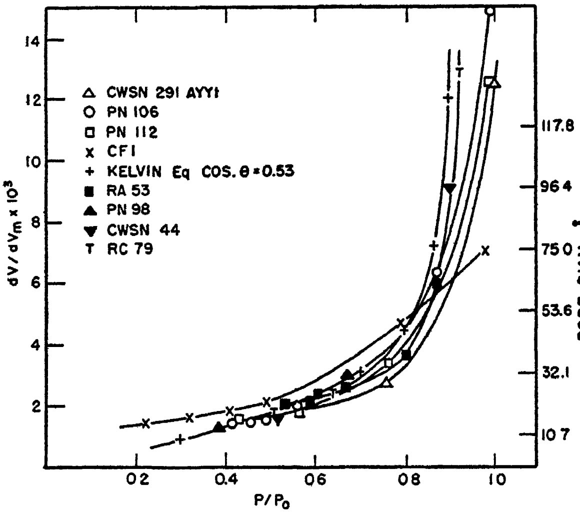


Fig. 21. Variation with p/p_0 of the pore diameters of charcoals as calculated from the curves of figure 20.

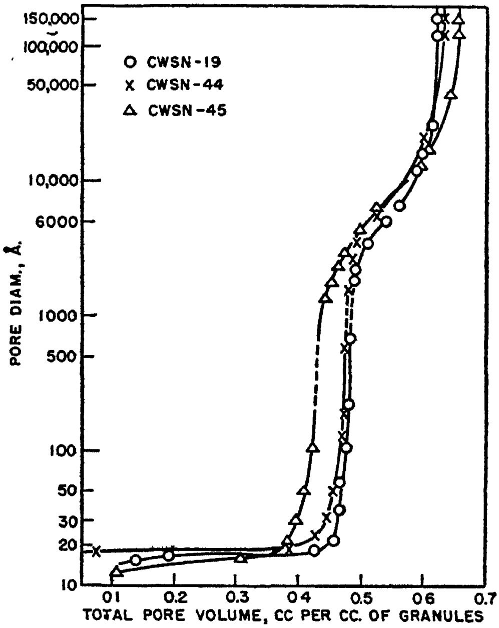


Fig. 22. Pore-diameter distribution of three charcoals (91) made by the zinc chloride process. The lower parts of the curves were obtained by measuring the change in surface area as a function of the amount of sorbed water; the upper part was measured by a mercury porosimeter (90, 91).

gassed carbon black, it seems probable that at a relative pressure of 0.9 the portion of the charcoal not covered by capillary condensation has at least a monolayer of adsorbed water vapor on it. Hence, the angle of wetting is likely to be much more nearly zero than for lower relative pressures where no such film exists. One would therefore expect that cos θ above relative pressures of 0.9 might equal unity. Probably the lack of agreement (above about 0.9 relative pressure) of the Kelvin equation with results obtained by equation 14 is due much more to the difficulty of applying equation 14 accurately to that part of the isotherm corresponding to the pores larger than about 100 Å. Presumably, the objection to interpreting the water isotherms in this way has to do with the lack of smoothness with which the pore diameter *vs.* pore volume curves such as shown in figure 22 extrapolate from the lower pore-diameter range into the curves for the higher range determined by the mercury method discussed below. At any rate, Juhola has elected to leave the region between about 100 Å. and 2000 Å. diameters as undetermined in most of the materials he has studied.

In the application of the Kelvin equation to water-desorption isotherms for measurements of pore diameter, the cos θ term has been considered as taking into account only the angle of wetting. Actually, it may perhaps be a constant that is taking into consideration any variation in the surface tensions (σ), the molar volume (V), or the angle of wetting in the small-pore regions where we have no direct information as to the validity of the values for these terms as determined from bulk water.

The choice of the value of 0.53 for cos θ is, as pointed out by Juhola (90), attended with considerable uncertainty. Depending upon the density selected for water and for the adsorbed nitrogen in the experimental work, this cos θ term might vary from 0.44 to 0.58. Nevertheless, for those charcoals in which there is negligible water adsorption at relative pressures below about 0.4, the method appears to give very reasonable values for pore diameters. Distribution curves for about 110 charcoals or charcoal-producing materials are given by Juhola in his final NDRC report (90).

E. Measurement of pore size by the high-pressure mercury method

Washburn (147) was the first to suggest that one could measure the diameter of pores by measuring the pressure necessary to force mercury into them. It can be shown that the diameter of a cylindrical capillary is related to the density, p, and surface tension, σ, of mercury, by the equation

$$D = \frac{4\sigma \cos \theta}{phg} \qquad (15)$$

where θ is the angle of wetting,[7] h is the pressure applied, and g is the gravitational constant. This method was selected and applied (63) to a number of charcoals using pressures up to 100 atm. in some of the early war work at Johns Hopkins University; it has been much more extensively studied and applied by Juhola (90) on more than a hundred charcoals. As a matter of fact Juhola (90) tested the method (151) on a block of briquetted, carbonized coconut shell charcoal by boring a hole 0.015 in. (3.81 × 10^6 Å.) in diameter and measuring the pressure required to force mercury through it. Four runs, calculated by equation 15, gave results of 3.39, 3.96, 3.43, and 3.75 × 10^6 Å., which agree well with the actual value, 3.81 × 10^6 Å.

---

[7] Obviously, the value of D from equation 15 will depend on the exact value of θ, the wetting angle. Ritter and Drake (47, 134) measured this angle for numerous solids and found 140° as a representative value. This means that the pore diameters reported by them are about 0.78 as large as they would be if θ had been assumed to be 180°.

Juhola (89) made measurements by the mercury method in glass capillaries as small as 100,000 Å. and reported a value for cos θ of 0.78 as giving good agreement between the mercury method and independent pore-diameter measurements. In spite of this, all charcoal work by Juhola (89, 90) and by other NDRC groups (63) reported in the present paper is based on the assumption of 180° for θ.

Recently, Ritter and Drake (47, 134) have published details of the method as applied to cracking catalysts and also to a number of commercially available charcoals. Their runs have extended up to 10,000 pounds per square inch pressure and therefore include measurements to pore diameters as small as 200 Å. diameter. A number of their resulting curves are shown in figures 23 and 24.

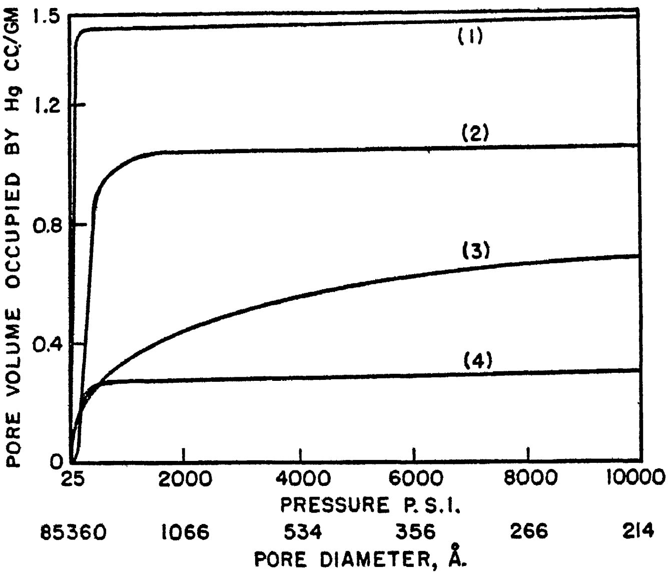


FIG. 23. Pore-size distributions as determined by Ritter and Drake (47, 134) by the high-pressure mercury method for diatomaceous earth (curves 1 and 2), Darco carbon (curve 3), and Columbia carbon (curve 4).

Several inherent characteristics of the mercury method should be noted. If bottleneck capillaries exist, it must be realized that the pore diameter measured will be that of the narrow neck rather than the larger bulk of the capillary. Accordingly, on an average, one would expect that the pore diameters obtained by the mercury method will be somewhat too small, or that the pore volume for a given pore size by the mercury method will be too large. This would mean that the curves in figures 23 and 24 should all be shifted to somewhat larger pore sizes if some method were available for estimating the difference on an average between the narrow necks and the larger main portion of the bottleneck-shaped capillaries. In agreement with this explanation, the few measurements (59, 59a) on nitrogen adsorption in the relative pressure range 0.99–0.999 corresponding to pore sizes from 1800 to 18,000 Å. show much smaller volumes for a given pore size than are shown by the mercury runs. A comparison on seven charcoals is shown in table 4.

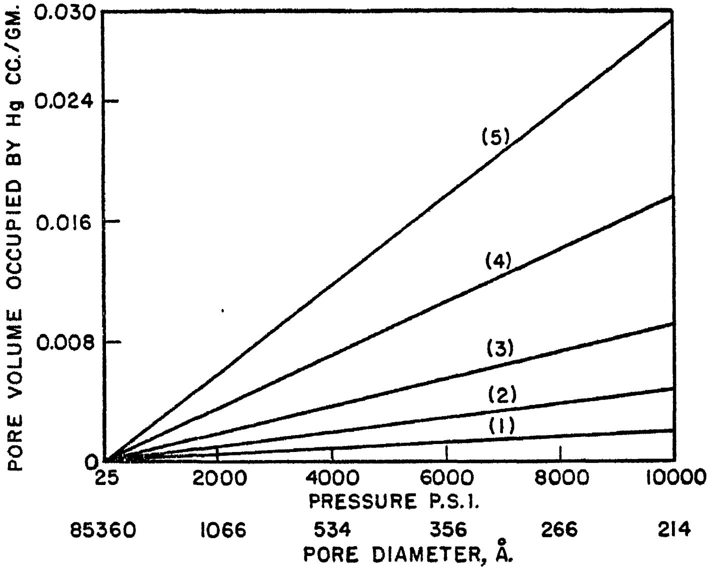


Fig. 24. Pore-size distribution as determined by Ritter and Drake (47, 134) by the high-pressure mercury method for five different silica-alumina gel catalysts.

TABLE 4

Macropore volume in the 1800–18,000 Å. diameter range

CHARCOAL	PORE VOLUME IN CC. PER GRAM	
	By nitrogen adsorption	By mercury method*
CWSN 19	0.04	0.148
CWSN 196 B1X	0.042	0.308
CWSN 196 B1X TH 427	0.039	0.327
CWSN 196 B1X TH 410	0.050	0.301
NDRC SI 26	0.006	0.0044
CFI "CC"	0.0016	0.019
PCI P58	0.062	0.106

* Using $\theta = 180°$ in equation 15.

Another method for judging the mercury method is illustrated by table 5 for these same seven charcoals. According to equation 12, nitrogen at a relative pressure of 0.99 should fill all pores up to about 1800 Å. in diameter. The pore volume then remaining free of the condensed nitrogen (called "free volume" in table 5) should then agree with the volume of mercury forced into the charcoals by 100 atm. pressure, since this pressure corresponds approximately to pores having diameters equal to or larger than 1800 Å. if $\theta = 180°$ in equation 15. The agreement shown in table 5 is as good as can be expected, since the "free volume" values may be too low if the density of liquid nitrogen in the capillaries is greater than the assumed value of 0.808; while the value by the mercury method may be too high because of pores larger than 100,000 Å. being connected to the outside of the particles by bottlenecks in the size range 1800–180,000 Å. The mercury values will also be too high if θ for mercury in contact with charcoal should be 140° instead of 180°; the mercury values, on the other hand, could be too low if any large capillaries are connected to the surface by capillaries smaller than 1800 Å.

The mercury pore-measuring experiments are accompanied (90) by a hysteresis which, for devolatilized or activated charcoals or charcoal materials, is usually equal to 90–95 per cent of the mercury in the pores. On the other hand, some of the baked charcoal stocks prior to activation show as little as 35 per cent of the total mercury in the sample retained when the pressure is released. It is a curious fact that the samples showing the smaller mercury hysteresis are also those that show little or no water hysteresis. Juhola (90) has suggested that this may be interpreted as evidence for the formation of "bottleneck" pores during activation, the narrow constrictions in the small pores being responsible for the water hysteresis, and the narrow constrictions in the larger pores for mercury hysteresis.

TABLE 5

"Free volume" of charcoals compared to macropore volume to 100 atm. by mercury method*

CHARCOALS	"FREE VOLUME"	VOLUME BY MERCURY METHOD TO 100 ATM.†
	cc./gram	*cc /gram*
CWSN 19	0.162	0.199
CWSN 196 B1X	0.402	0.475
CWSN 196 B1X TH 427	0.482	0.491
CWSN 196 B1X TH 410	0.467	0.461
NDRC SI 26	0.007	0.026
CFI "CC"	0.009	0.050
PCI P58	0.265	0.304

* "Free volume" is the difference between the total pore volume and the nitrogen adsorption at 0.99 relative pressure (calculated as liquid).

† Using $\theta = 180°$ in equation 15.

V. PORE-SIZE ALTERATION

The possibility of a relation between pore distribution and the effectiveness of gas mask charcoal (156) naturally led to a detailed study of ways and means of altering pore size and distribution in adsorbents. The relation between the findings and the production of effective gas mask charcoals cannot be discussed here. Nevertheless, the influence of certain treatments on pore distribution seems of sufficient interest to warrant inclusion in this paper (83).

The alteration in pore size has been judged mostly by the change in the appearance of the nitrogen-adsorption isotherms up to relative pressures of 0.99 (62). In discussing the influence of various factors on the shapes of the isotherms, it will be convenient to differentiate between the total adsorption in the relative pressure region (called *AB*) up to 0.4, the slope of the isotherm in the region between 0.4 and 0.7 (called *BC*; this is roughly the pore size that would be filled with water vapor by capillary condensation at 80 per cent relative humidity if cos θ for water on charcoal is about 0.6), and the slope of the isotherm in the region 0.7 and 0.99 (called *CD*; this region is the portion of the macropore region having diameters between about 52 and 1850 Å. according to equation 12).

It is also important to differentiate between changes in isotherms per gram of charcoal and changes per cubic centimeter of granules (this means per cubic centimeter of actual charcoal volume as measured by mercury pycnometers at 1 atm. pressure).

In a general way it can be said that it is possible (58, 83) to tailor-make the pore distributions in charcoals by a combination of steaming and hydrogenating with and without impregnants. The region *AB* can be increased or decreased on either a per gram or a per cubic centimeter basis; the slope of the isotherms in both the *BC* and *CD* regions can be left unchanged or increased. An increase in slope of either of these last two regions is interpreted as an increase in pore volume in these respective ranges. On the other hand, an increase in *AB* might mean an increase in the number of small pores or it might mean an increase in the total surface area caused possibly by increases in the number of pores in the *BC* region.

In figures 25, 26, and 27 are shown a few typical examples (58, 83) of the effect of steaming, air oxidizing, hydrogenating and, to a limited extent, treating with impregnants. For more details and for examples not included here the reader is referred to a paper by Holmes and Emmett (83) containing all of the results that were obtained on pore alteration. Below is discussed the influence of a few of the operations on the shape of the isotherms insofar as any general conclusions can be drawn.

A. Steaming without impregnation

Moderate steaming at 750°C. on standard charcoal samples increased the adsorption in region *AB*. This presumably means that added steaming beyond the point usually used for steam-activated charcoals continues to open up small pores. This was always true on a weight basis on the four charcoals studied: CWSN 19, CWSN S5, coconut charcoal, and PCI P58. The adsorption per cubic centimeter was increased in the *AB* region for the first of these four but decreases slightly for the other three. Examples for some of these charcoals are given by curves in figures 25, 26, and 27. There is nothing unusual in these steaming results, since new small pores can certainly be opened up by the treatment with a resulting increase in adsorption per gram. If the steaming is carried too far, of course, the adsorption per cubic centimeter of granules must start to decrease because of overlapping of the small pores. Also, if considerable portions of the charcoal are removed by steaming along the walls of capillaries larger than 1860 Å. in diameter the adsorption per cubic centimeter can be greatly lowered without affecting the adsorption per gram.

B. Hydrogenation without impregnation

It does not seem to be generally recognized in the literature that hydrogenation can alter pore sizes and distribution just as effectively as can steaming. Usually, however, a somewhat higher temperature is needed for hydrogenation than for steaming. In figures 25, 26, and 27 are shown curves illustrating the effect of hydrogenation on two of the charcoals studied. For all of them, the adsorption in the *AB* region per gram either increases or remains constant; the slope of the adsorption in the intermediate *BC* region remains unchanged; and the slope of the adsorption in the *CD* region increases sharply with an especially rapid increase close to a relative pressure of 0.99. In fact, the rapid rise in the adsorption between 0.9 and 0.99 relative pressure is rather characteristic of hydrogenation in the absence of impregnants.

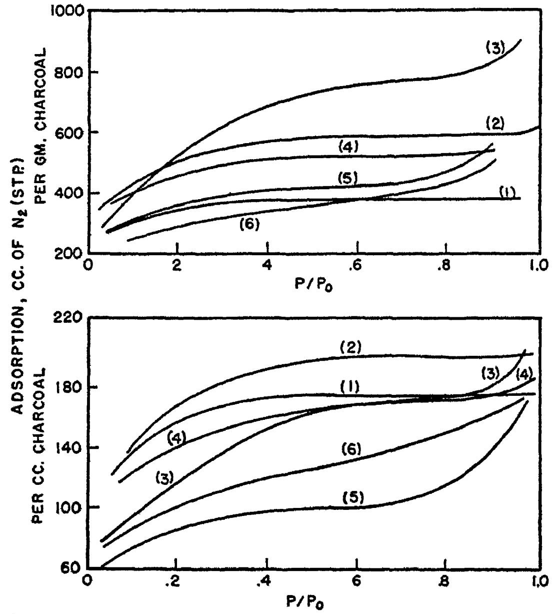


FIG. 25. Nitrogen isotherms showing pore alterations on charcoal CWSN 19 as follows:

Curve 1. Normal CWSN 19

Curve 2. Sample steamed at 750°C. to a 43 per cent loss

Curve 3. Hydrogenated at 1000°C. to 74 per cent loss

Curve 4. Impregnated with 5 per cent Fe_2O_3 and steamed at 750°C. to 37 per cent loss

Curve 5. Impregnated with 5 per cent Fe_2O_3 and hydrogenated at 600°C. to 50 per cent loss

Curve 6. Impregnated with 5 per cent Fe_2O_3 and air oxidized at 350°C. to 48 per cent loss

Only for charcoal CWSN 19 is there an increase in the total adsorption per cubic centimeter of granules during mild hydrogenation. Presumably, the major attack is on pores in the *CD* region.

C. Partial combustion in nitrogen containing limited amounts of oxygen and no impregnants

Mild oxidation on CWSN 19 increased the adsorption in the *AB* region by a small amount both on a per gram and a per cubic centimeter basis. On the other hand, it had little influence on the slope of the isotherm above 0.4 relative presure. Presumably such oxidation primarily effects the formation of new pores (83).

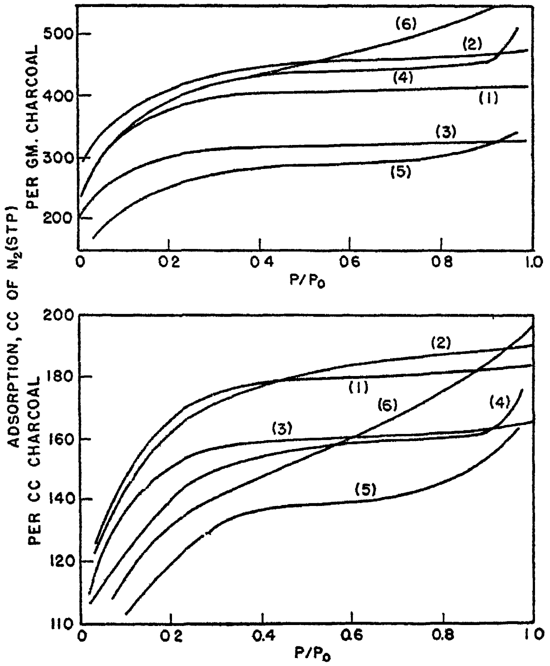


FIG. 26. Nitrogen isotherms showing pore alterations on charcoal CWSN S5 as follows:

Curve 1.	Normal CWSN S5
Curve 2.	Sample heated in pure nitrogen to 1200°C. and then steamed at 750°C. to 69 per cent loss
Curve 3.	Heated for 2 hr. in pure nitrogen at 1200°C.
Curve 4.	Hydrogenated at 1000°C. to 37 per cent loss
Curve 5.	Impregnated with 5 per cent Fe_2O_3 and treated with tank nitrogen at 1000°C. to 25 per cent loss
Curve 6.	Impregnated with 5 per cent Fe_2O_3 and hydrogenated at 600°C. to 30 per cent loss

D. Influence of impregnants on steaming, hydrogenation, and partial oxidation

In the course of the work the action of chromic oxide, ferric oxide, molybdic oxide, sodium carbonate, and cupric oxide on the various processes for altering pore size was studied. These compounds were formed in amounts ranging from

0.2 to 5.0 per cent by various procedures, as described by Holmes and Emmett (83). It is difficult to generalize in regard to the effects noted, because the impregnant at times produced results that differed as a function of the particular compounds used in getting the given oxide on the sample. However, in a general way the results were as follows:

(*1*) Fe_2O_3 gave definite evidence of catalyzing the attack on the charcoal. For example, at 600°C. in the presence of 5 per cent ferric oxide impregnant a 50 per cent weight loss of CWSN 19 was brought about by hydrogenation, whereas in the absence of the impregnant practically no loss occurred. Another evidence is the fact that even on a weight basis, the adsorption up to 0.4 relative pressure decreased in a majority of treatments with ferric oxide as impregnant. This is definite evidence of an attack on the smaller pores greater in extent than any formation of small pores that is taking place. The ferric oxide invariably causes a considerable rise in the isotherms between 0.7 and 0.99, regardless of the gas being employed for activation.

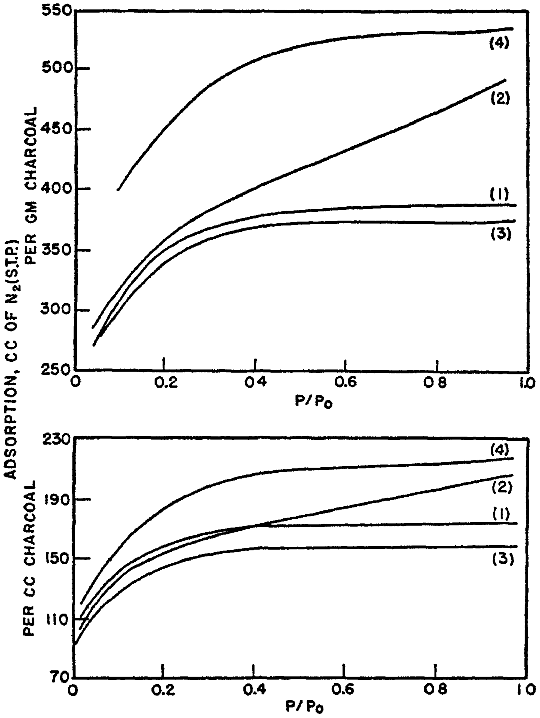


FIG. 27. Nitrogen isotherms showing pore alterations on CWSN 19 produced by hydrogenation as follows:

Curve 1. Normal CWSN 19

Curve 2. Impregnation with 5 per cent NiO from nickel nitrate, followed by hydrogenation at 1000°C. to 27 per cent loss

Curve 3. Impregnation with NiO from nickel chloride followed by hydrogenation at 1000°C. to a 25 per cent loss

Curve 4. Hydrogenation at 1000°C. to a 26 per cent loss

One result with ferric oxide is especially noteworthy (83). In a run using 5 per cent ferric oxide and carried out with tank nitrogen at 1000°C. to a 13 per cent weight loss, the total pore volume on both the per gram and per cubic centimeter basis dropped about 20 per cent. This means the closing up of enough small pores either by plugging with impregnants or by the effect of treating to 1000°C. to more than compensate for the increase in the number of pores indicated by the 0.7–0.99 relative pressure region. This is the only instance in which on CWSN 19 positive evidence was obtained of a pore-closing or pore-plugging effect.

(*2*) Impregnation with Cr_2O_3 combined with steaming seems to have little added effect over steaming by itself, on CWSN 19. On hydrogenation, however, the effect is similar to that of the iron in that a considerable decrease in the *AB* region occurs on a volume basis with a marked increase in the *CD* region (83).

The results on CWSN S5 are confused by the fact that heating this charcoal to 1200°C. even in pure nitrogen (figure 26) causes a shrinkage, the result of which is that the adsorption per unit weight decreases *more* than the adsorption per unit volume. This would be expected if the shrinkage causes an increase in the apparent particle density. At 750°C. steaming after impregnation with chromic oxide produces a very different effect from steaming alone. The low-pressure adsorption increases per cubic centimeter of charcoal, whereas the slopes of the *BC* and *CD* regions are both increased by about 15 per cent (83). The hydrogenation at 1000°C. with chromic oxide present seems to produce the same sintering effect caused by heating this charcoal to 1200°C., but in addition causes a 20 per cent increase in the slope of the *CD* portion of the isotherm (83).

Steaming coconut charcoal impregnated with 0.2 per cent chromic oxide caused nearly a 100 per cent increase in the adsorption up to 0.4 relative pressure on a weight basis, a 30 per cent increase on a volume basis, and a 15 per cent slope increase in the *CD* region. Presumably, the chromic oxide catalyzed the burning away of pore walls to make larger capillaries and also the formation of new small capillaries. Strangely enough, 5 per cent chromic oxide and steaming produced very little more effect than straight steaming to a similar weight loss, though the slopes of the *BC* and *CD* regions were 10–20 per cent greater than those resulting from steaming alone. Hydrogenation of coconut charcoal impregnated with 0.2 or 5 per cent chromic oxide caused none of the slope change (83) characterizing similar runs on CWSN 19 or CWSN S5, the slope of the isotherms being identical with that of the original charcoal and the absolute adsorption values a little lower; in fact the marked turn-up of the isotherm between 0.9 and 0.99 produced by straight hydrogenation is absent when chromic oxide is present.

PCI P58 impregnated with chromic oxide behaved little differently on steaming from samples not impregnated as regards the slope of the isotherms; however, the larger (5 per cent) chromic oxide content caused a drop in the absolute adsorption of 15 or 20 per cent on both the weight and the volume basis. Hydrogenation after impregnation with chromic oxide produced the same slope increase in the *CD* region that was obtained without any impregnation; the total pore volume, however, of this charcoal was decreased by the impregnation both on the weight and the volume basis, much as though a pore plugging had taken place that decreased the adsorption on both a weight and a volume basis.

In a word, it is apparent that chromic oxide as an impregnant can effect marked changes in charcoals when combined with steaming and hydrogenation, though the effects are apparently quite specific and dependent on the kind of charcoal used.

(*3*) NiO on CWSN 19 produces on steaming no change in slope of the isotherms, just as was true of straight steaming; however, it appears (83) to drop the total pore volume on both a weight and a volume basis by about 35 per cent compared to the volume after steaming in the absence of nickelous oxide. For hydrogenation, the nickel results are especially noteworthy in that they show a decided specificity upon the particular nickel salt used in impregnation. For example, if the nitrate is used together with precipitation by ammonium hydroxide, hydrogenation to a weight loss of 27 per cent results in a nitrogen isotherm that is a straight line from 0.4 to 0.99 relative pressure with an increase in volume of 20 per cent over this range. In contrast to this, the same per cent of nickelous oxide produced from nickel chloride plus ammonium hydroxide caused no change in slope and only a few per cent decrease in total adsorption compared to the initial CWSN 19 (figure 27), thus apparently having little effect on the hydrogenation.

On CWSN S5 the single experiment tried indicated that impregnation with 5 per cent nickelous oxide combined with hydrogenation at 1000°C. resulted in no change in slope of the isotherm compared to the original and a decrease of about 15 per cent total adsorption on both a weight and a volume basis (83).

(*4*) Impregnation with 5 per cent Mo_2O_3 produced no specific effects in either steaming or hydrogenating CWSN 19 other than those observed without the impregnation. Likewise, 5 per cent sodium oxide from sodium carbonate produced no noticeable modification in the hydrogenation of CWSN 19 at 1000°C.

(*5*) The two experiments on steaming type A whetlerites (copper impregnation) behaved quite differently. On CWSN 19, steaming whetlerite to 26 per cent loss at 750°C. left the isotherm unchanged in slope from the original charcoal but about 35 per cent smaller in volume than would have resulted from a steaming to a 40 per cent weight loss in the absence of the impregnant. On the other hand, steaming type A whetlerite made from CWSN S5 caused the slope of the *BC* and *CD* sections of the isotherm to increase greatly, the adsorption at 0.99 relative pressure being about 20 per cent greater than at 0.4 relative pressure.

VI. OXYGEN SURFACE COMPLEXES ON CHARCOALS

A. *Introduction*

It has long been known (45, 103, 112, 113, 114, 121), that charcoals and activated carbons are covered with carbon–oxygen complexes, the composition of which varies as a function of the method of treatment of the sample. Research on surface complexes of charcoal during the war has been carried out primarily because of the help it might furnish in (*a*) showing the proper surface treatment to give maximum adsorption of certain gases such as ammonia that are apparently very sensitive to the nature of the charcoal surface, (*b*) interpreting the aging of base charcoal that from time to time was thought to be taking place on storage under humid conditions, and (*c*) indicating the type of surface complex that might be most effective in any desired minimizing of the adsorption of water vapor, especially at high relative humidities.

The actual results obtained that are applicable to the three main objects of the work are, for the most part, restricted to item (*a*) above. The surface complex studies failed to throw much light on item (*b*) (59). As for (*c*), the behavior of charcoal and whetlerites toward water vapor appears to be much more dependent on the pore-size distribution in the region between 0.8 and 0.99 relative pressure than it does on the nature of the surface complex. The latter is more likely to influence the amount of water adsorption occurring at low relative pressures but is less influential on the adsorption at high relative pressures.

The work that has been done on the surface complexes divides itself rather naturally into two parts: (*1*) the study of oxygen adsorption by the charcoal in relation to the adsorptive properties toward ammonia, acids, and bases; and (*2*) the measurement of the gas evolution as a function of the temperature to which the various charcoals have been heated. The first of these two groups of experiments was carried out chiefly by Young (153, 154) and his coworkers; the second by Anderson (13, 59). These two researches contribute a great many useful data and correlations that will now be briefly summarized.

B. Oxygen adsorption by charcoals and its influence on their properties

As pointed out by Young (153), the existence of several different carbon–oxygen surface complexes on charcoal and carbon black has been claimed in the literature (102, 105, 132, 136, 137, 141, 143). Two (105, 136, 137) of these appear to be formed by the picking up of oxygen at room temperature; another is said to be formed by exposure of charcoal to oxygen at about 400°C.; and a fourth (95) is supposed to form above 850°C. in the presence of oxidizing gases. Oxygen complexes have been reported for graphite and diamond (17) as well as for charcoal and carbon black. The experiments reviewed and summarized in the present section were directed not so much toward the verification of these various complexes as toward the study of the influence of the complexes formed at 400°C. in free oxygen upon the properties of the various charcoals as adsorbents for acids, bases, ammonia, hydrogen chloride, and water vapor. Some few experiments were also made upon the rate of oxygen pickup by various charcoals at room temperature. The various results and observations made during this work may be summarized as follows:

1. Oxygen pickup by charcoals

Lowry (112) pointed out that oxygen is slowly picked up by charcoals at room temperature in the form of a chemical adsorption. The equilibrium pressure of this tightly bound oxygen is substantially zero at room temperature (118). In addition there is a rapid physical adsorption which is easily reversible and which amounts to about 10 per cent of a monolayer at 1 atm. pressure. The slow chemical adsorption varies in amount and rate with different charcoals. In figure 28 are shown the results obtained by Young (153) on a typical group of charcoals. The total oxygen picked up irreversibly by even CWSN 44 is apparently only a very small fraction of a monolayer.

By exposing charcoals to oxygen at 400°C. Young has succeeded in building up an oxygen content of as much as 18 per cent on the charcoals. This oxygen coating was accompanied by a 56 per cent weight loss. It should be noted that even 18 per cent oxygen corresponds to only about a monolayer of oxygen on the surface of the carbon.

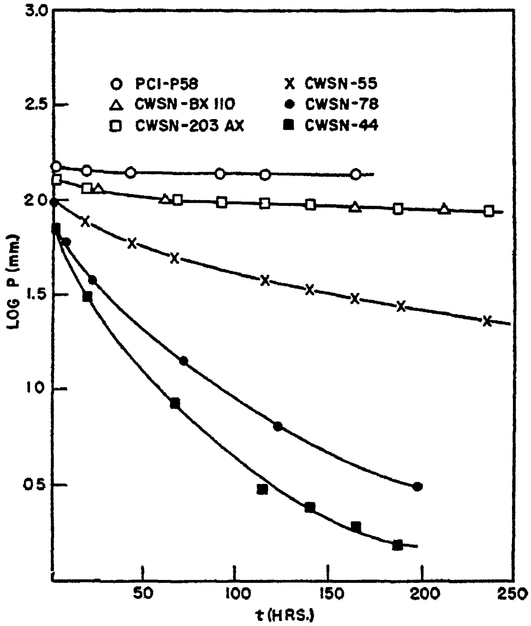
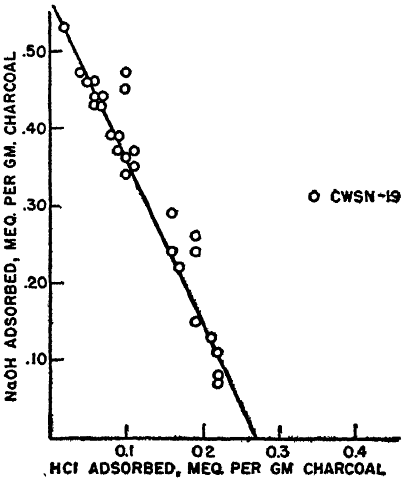


FIG. 28. Rate of oxygen chemisorption at 25°C. by charcoal samples

2. Influence of oxygen treatment on the base and acid adsorptive properties

CWSN 19, upon which most of the oxygen complex work has been done, originally adsorbed (153) 0.27 milliequivalent of hydrochloric acid per gram and no sodium hydroxide. The time allowed for equilibration in adsorption in these experiments was 30 min., and the original concentration of the adsorbate solution was 0.03 *N*. Treating the charcoal with oxygen increased the base adsorption and decreased the acid adsorption. The results shown in figure 29 are taken from the paper of Young (153). In the same figure is shown the sodium hydroxide adsorption as a function of the weight loss in the oxidation process.

In figure 30 is shown the variation of the rate of pickup of sodium hydroxide with time, temperature, and the amount of crushing to which the sample has been subjected. Evidently, crushing the sample increases greatly the rate of adsorption, as does also increasing the temperature. Neither temperature increase nor crushing has any effect on the final equilibrium value of the adsorption. In figure 30, also, is shown the adsorption curve obtained by allowing 24 hr. equilibration and by using adsorption solutions that were 0.5 *N*. As pointed out by Young, the slope of this curve indicates that for every equivalent of acid-forming power lost by the charcoal, four to five equivalents of base-forming power are gained.



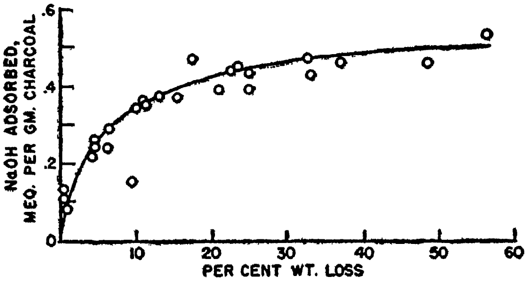
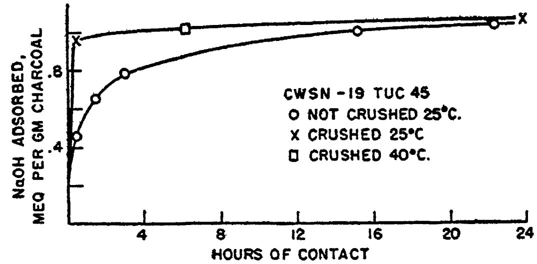


FIG. 29A (top). Plot of the adsorption of sodium hydroxide against that of hydrochloric acid on charcoal samples treated with oxygen at 400°C. (153).

FIG. 29B (bottom). Plot of the adsorption of sodium hydroxide against the weight loss of the sample of charcoal during oxidation (153).

Experiments by King (95) and also by Young (153) lead to the conclusion that both the H^+ and the Cl^- are adsorbed from solutions by the charcoals. Also, both Na^+ and OH^- are adsorbed. It is still unknown whether the alkali "adsorption" is a process in which the Na^+ by base exchange displaces an H^+ from the surface which then reacts with the OH^- or whether the Na^+ and OH^- are actually adsorbed.

Washing experiments showed that most of the hydrochloric acid adsorbed by the untreated CWSN 19 and most of the sodium hydroxide adsorbed by the oxygen-treated samples were irreversibly adsorbed. In other words, they were not removed by thorough washing. However, these quantities of "irreversibly held" adsorbates could be titrated with base and acid, respectively. The samples could then be washed and caused to readsorb the original amount of adsorbate. For example, the original CWSN 19 held 0.24 milliequivalent of hydrochloric acid irreversibly. This, on titration, picked up 0.24 milliequivalent of sodium hydroxide with the evolution of this amount of sodium chloride into the solution. The sample after washing could then pick up 0.24 milliequivalent of hydrochloric acid and the process could be repeated.



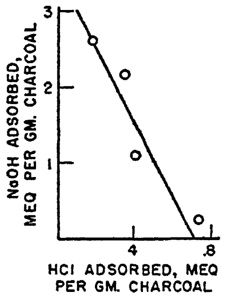


FIG. 30A (top). Adsorption of sodium hydroxide as a function of the time of contact between the solution and the charcoal.

FIG. 30B (bottom). Comparison of the sodium hydroxide and hydrochloric acid adsorption by oxygen-treated charcoal on 24-hr. exposure of the charcoal to 0.5 N solutions.

3. Influence of surface complex on the adsorption of water vapor

It has already been pointed out in the section on water adsorption that adding oxygen complex to a charcoal increases the low-pressure adsorption of water vapor and displaces the desorption hysteresis loop to lower relative pressures. Conversely, treating charcoals with hydrogen or with steam at high temperature tends to shift the adsorption curves to higher relative pressure and decreases markedly the adsorption below 0.5 relative pressure. It should also be noted that similar effects have been observed for carbon black samples, as shown in figure 13.

4. Influence of surface complex on the adsorption of ammonia and of hydrogen chloride

Treating a charcoal with oxygen at 400°C. increases the ammonia adsorption over the entire relative pressure range (65, 153). In figure 31 are shown two typical curves that illustrate the effect of oxygen coating. The extra ammonia pickup would appear to be due to a kind of chemical adsorption of ammonia, since the increase in adsorption is between 75 and 100 cc. throughout the entire pressure range. However, the heat of binding of such chemisorption is not great, as is evidenced by the fact that the extra ammonia will pump off slowly at 25°C. and completely in a short time at 100°C. (65). It should also be recorded that nitrogen isotherms prove that this enhanced ammonia adsorption is definitely not the result of an increase in surface of the charcoal resulting from the oxygen treatment. It is due to the specific nature of the surface containing the oxygen complex.

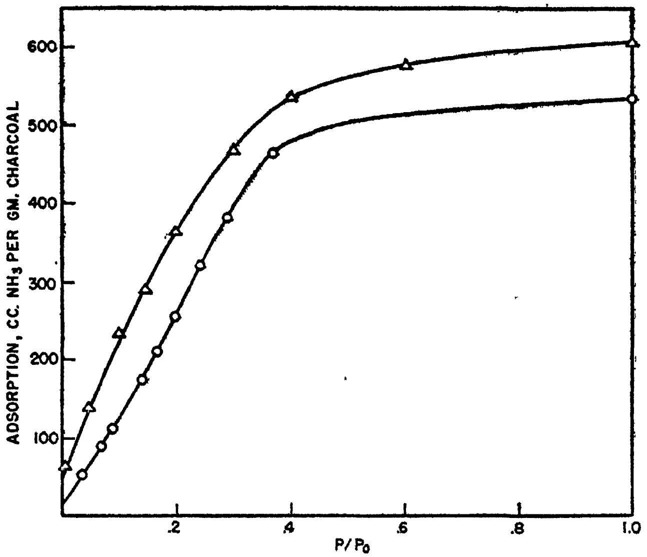


FIG. 31. Adsorption isotherm for ammonia at −46°C. on a sample of CWSN 19 TUC 742 (circles) and on a sample of this charcoal after it had been subjected to surface oxidation by free oxygen at 400°C. (triangles).

The adsorption of hydrogen chloride gas by CWSN 19 is not altered (52) in any marked way by oxygen coating. The changes in the adsorption are small and apparently no greater than the corresponding changes in the nitrogen adsorption.

5. Heat of binding of oxygen to carbon in the surface complex

By a series of careful measurements on the heat of combustion of charcoal as a function of the amount of oxygen complex on the surface, Young (153) has been able to show that the oxygen is held to the surface of a carbon by a heat of about 60,000–65,000 cal. per mole of oxygen. The heat of adsorption at 400°C. thus estimated appears to be independent of the fraction of the surface covered by complex. These heat of adsorption values are in good agreement with the following values: 70,000 cal. found by Keyes and Marshall (94) for charcoal at 0°C., 60,000 cal. reported by Blanch and Garner (25) for adsorption at room temperature, 70,000 cal. found by McKie at 20°C. (122), and 70,000–129,000 cal. reported by Marshall and MacInnes (119). There can be no doubt that the oxygen is held to the carbon surface by very strong chemical bonds (1, 93).

C. Gas evolution from charcoals as a function of the temperature to which they are heated

Lowry (112) has described the apparatus used and the results obtained in degassing a series of charcoals which at the end of World War I may be considered as typical of those used by the United States, Great Britain, and Germany. In general, he showed that all charcoals evolved considerable quantities of carbon monoxide, carbon dioxide, and water vapor up to about 900°C. Between 900 and 1200°C. increasingly large quantities of hydrogen were given off. Part of this hydrogen appeared to come from the surface of the charcoal, though it is also possible that part of it resulted from decomposition of hydrogen–carbon complexes that were not located at the actual surface of the charcoal.

Using a very similar apparatus, Anderson (13, 59) has carried out an extended series of experiments on various charcoals of interest in the recent research work in World War II. The evolved gas was collected during periods of about 7 hr. for each temperature interval studied. The experiments were grouped to cover the range 25–300°C., 300–600°C., 600–900°C., and 900–1200°C. The variables studied included the nature of the charcoal, the ash content (150) of the charcoal, and the type of treatment to which the charcoal had been subjected. The principal results (59) obtained may be briefly summarized as follows:

(*1*) In table 6 are shown the volumes of carbon monoxide, hydrogen, carbon dioxide, methane, and water evolved from a number of typical charcoals as a function of the temperature to which they were heated. In table 7 the results are summarized to cover the region up to 900°C. and up to 1200°C.; in this latter table also are shown the results of gas evolution to 1200°C., calculated in terms of equivalent per cent hydrogen and oxygen in the original charcoal. For comparison is also shown the per cent oxygen present in the ash wherever ash analysis was available or could be guessed from the method of preparation of the charcoal.

Several general conclusions can be drawn from the results in these two tables. In the first place it should be noted that the evolution of carbon monoxide and carbon dioxide is smaller from the PCI, CWSC, CFI, and CWSB X (nut shell) than from the CWSN samples prepared by the zinc chloride process. However, a detailed study (13) of the gas evolution from one of the samples, CWSN S5, at 60° intervals showed that most of the carbon monoxide and water were evolved in the temperature range 600–800°C. Concomitantly with the gas burst, a deposit of zinc metal was formed on the cooler part of the reaction vessel. In all probability, therefore, the excessive evolution of carbon monoxide and water from the CWSN samples in the temperature range up to 900°C. may be attributed to a large extent to the reduction of zinc oxide ash by carbon and by hydrogen. Consistent with this interpretation is the fact that CWSN 19, which had only 0.2 per cent ash, yielded volumes of carbon monoxide and water in the temperature range up to 900°C. approximately the same as obtained from charcoals not made by the zinc chloride process.

At temperatures above 900°C., a burst of carbon monoxide was obtained from all of the charcoals that had appreciable percentages of ash other than zinc oxide. There seems to be little doubt but that this higher temperature evolution of carbon monoxide is caused by the reduction of the ash components by carbon.

TABLE 6

Degassing experiments on charcoals

SAMPLE	GAS EVOLVED, CC. (S.T.P.) PER GRAM																		
	25–300°C.			300–600°C.				600–900°C.				900–1200°C.				
	CO	CO_2	H_2O	H_2	CO	CO_2	H_2O	H_2	CO	CO_2	H_2O	H_2	CO	CH_4†	CO_2	H_2O
CWSN 19	0.2	0.3	0.4	0.3	3.8	1.5	1.3	10.4	11.7	0.5	0.4	46.4	1.0	2.1	1.0	0.0
CWSN S5	0.5	2.0	2.3	1.0	4.6	2.3	5.3	92.0	21.7	1.4	6.0	36.9	0.6	0.6	0.0	0.0
CWSN S5 (extracted with HF)	0.9	3.0	5.8	2.5	87.2	39.9	1.9	66.9	27.7	1.2	2.0	21.8	0.4	0.6	0.7	0.1
CWSN 44	0.7	3.3	3.5	1.4	6.6	3.2	4.6	97.5	22.8	1.1	4.0	51.8	2.6	3.3	0.1	0.0
CWSN 196 B1	0.5	2.7	3.3	1.4	5.5	3.0	4.6	93.0	29.5	0.5	1.8	36.5	0.5	0.8	0.2	0.0
CWSN 196 B1X	0.2	1.5	1.6	1.0	3.3	6.8	1.6	53.1	11.8	0.2	0.1	33.8	0.4	0.8	0.2	0.1
PCI P58	0.1	0.2	0.9	0.1	1.2	0.7	0.7	16.2	11.4	0.5	0.2	38.3	7.8	4.7	0.0	0.0
CWSC 1242	0.3	0.6	0.9	0.0	0.7	1.2	1.1	5.8	4.0	0.3	0.2	19.3	0.9	0.1	0.2	0.1
CFI "CC"	0.1	0.2	1.2	0.0	0.7	0.3	1.1	7.8	5.5	0.2	0.2	38.5	63.4	0.8	0.2	0.0
CWSB X2	0.2	3.1	2.3					13.4*	7.8*	2.2*	1.9*	36.3	5.4	0.6	0.3	0.1
	25–120°C.			120–600°C.												
PCI P25	0.0	0.0	0.5	0.5	2.0	1.0	3.0	10.5	9.9	0.4	0.5	35.3	88.5	2.7	0.3	0.0
PCI P1042	0.0	0.2	0.6	0.3	2.6	1.2	1.3	7.5	9.6	0.3	0.3	43.2	93.1	2.3	0.4	0.0
PCI P1042 (extracted with HF)	0.0	0.0	0.7	0.6	51.2	9.4	4.3	20.8	20.9	3.0	0.3	22.3	0.8	0.8	0.4	0.0

* 300–900°C.

† Some methane was evolved below 900°C. Since the low-temperature formation was, however, small, it is not included in table 6. However, subtraction of the methane values for the 900–1200°C. range from those shown in table 7 for the 25–1200°C. region gives the total methane produced below 900°C. A similar procedure can be used in obtaining the amount of methane evolved below 900°C. in the samples shown in table 8.

Ash for the most part on analyzed samples was found to consist of silica and alumina (150). Data in the literature (30) indicate that for the reduction of silica by carbon to form silicon carbides and carbon monoxide, the partial pressure of evolved gas at 900°C. at equilibrium is about 0.1 mm. and at 1200°C. is about 10.7 mm. Accordingly, since the maximum pressure in the present experiments was about 0.02 mm. it is entirely possible that the evolution of carbon monoxide at higher temperature could have come from the reduction of silica components in the ash. In line with this conclusion is the fact that the gas evolved at temperatures in excess of 900°C. from a sample of PCI that had been rendered substantially ash free by extraction with hydrofluoric acid contained practically no carbon monoxide.

One other peculiarity of these results should be noted. Two different samples that had been extracted by hydrofluoric acid evolved excessive amounts of carbon monoxide and carbon dioxide in the region between 300° and 900°C. Thus, CWSN S5 after extraction evolved 115.8 cc. of carbon monoxide and 44.1 cc. of carbon dioxide, compared to 26.8 cc. of carbon monoxide and 5.7 cc. of carbon dioxide from the sample that had not been extracted. Corresponding results for PCI P1042 showed 72.1 cc. of carbon monoxide and 12.4 cc. of carbon dioxide after extraction, compared to 12.2 cc. of carbon monoxide and 1.5 cc. of carbon dioxide before extraction. The cause of this excessive evolution of gas from the extracted samples is not clear. Possibly, the reagents used have a catalytic effect on the oxidation of the surface by air during extraction or drying.

TABLE 7

Degassing experiments on charcoals

SAMPLE	TOTAL GAS EVOLVED, CC. (S.T.P.) PER GRAM									PER CENT BY WEIGHT OF		
	25–900°C.				25–1200°C.					H_2 evolved	O_2 evolved (as CO, CO_2, or H_2O)	O_2 in ash
	H_2	CO	CO_2	H_2O	H_2	CO	CH_4†	CO_2	H_2O			
CWSN 19	10.7	15.7	2.3	2.1	57.1	16.7	2.7	3.3	2.1	0.58	1.81	0.04*
CWSN S5	93.0	26.8	5.7	13.5	129.9	27.4	1.4	5.7	13.6	1.31	3.74	2.0 (118)
CWSN S5 (extracted with HF)	69.4	115.8	44.1	9.7	91.2	116.2	1.8	44.8	9.8	0.93	16.10	
CWSN 44	98.9	30.1	7.6	12.1	147.5	32.7	8.3	7.7	12.1	1.58	4.30	0.8*
CWSN 196 B1	94.4	35.5	6.2	9.7	130.9	36.0	1.8	6.4	9.8	1.29	4.18	0.6*
CWSN 196 B1X	54.1	15.3	8.5	3.3	87.9	15.7	1.5	8.7	3.4	0.84	2.59	1.0*
PCI P58	16.3	12.7	1.4	1.8	54.6	110.5	5.0	1.4	1.8	0.59	8.22	
CWSC 1242	5.8	5.0	2.1	2.1	25.1	5.9	0.2	2.3	2.3	0.25	0.91	
CFI "CC"	7.8	6.3	0.7	2.5	49.7	13.4	0.8	5.6	4.3	0.50	2.06	
CWSB X2	13.4	8.0	5.3	4.2	46.3	69.7	0.8	0.9	2.5	0.45	5.28	
PCI P25	11.0	11.9	1.4	4.0	46.3	100.5	2.8	1.7	4.0	0.40	7.70	
PCI P1042	7.8	12.2	1.7	2.2	51.0	102.3	2.5	2.1	2.2	0.58	7.76	
PCI P1042 (extracted with HF)	21.4	72.1	12.4	5.3	43.7	72.9	1.2	12.8	5.3	0.46	7.42	

* Ash was assumed to be zinc oxide in computation of these values.

† See footnote to table 6.

Strong evolution of hydrogen from certain charcoals was noted a number of years ago (112). The runs in tables 6 and 7 show that some of the charcoals evolve as much as 147 cc. of hydrogen per gram on being heated to 1200°C. In general, it appears that the zinc chloride charcoals evolved much more hydrogen than the others. Furthermore, with the exception of CWSN 19, all of the zinc chloride charcoals tested appeared to evolve most of their hydrogen in the 600–900°C. region rather than the 900–1200°C. region. CWSN 19, for some unknown reason, evolved the normal amount of hydrogen in the higher temperature region but very little hydrogen up to 900°C. The amount of hydrogen present in the charcoals is probably related to their pretreatment, since it is known that the higher the temperature of calcining of the various charcoals in the course of preparation and activation, the smaller the per cent of hydrogen that they contain. There is some evidence that steaming at 900°C. will put hydrogen onto a charcoal. Thus, a sample of CWSN 196 B1X that had been heat treated in nitrogen at 1000°C. until it would evolve only 15.6 cc. of hydrogen to 1200°C., was found to evolve 47 cc. of hydrogen after being steamed at 900°C. to a 56 per cent weight loss. In contrast to this, short steaming to a few per cent weight loss at 300°, 400°, and 750°C. caused no appreciable increase in the evolution of hydrogen above the 15.6 cc. of the original sample (13). There is a chance, of course, that the excessive steaming made possible the escape of some hydrogen that originally was buried so deep in the charcoal as not to be able to escape at temperatures up to 1200°C. Hence, the interpretation of this result must remain uncertain until more work is done.

(*2*) Heat treating samples of charcoal to 1000°C. in a stream of nitrogen was found (13, 59) to remove practically all of the carbon monoxide, carbon dioxide, and water from the surface and about two-thirds of the hydrogen. This would be expected on the basis of the degassing experiments shown in tables 6 and 7 and hence needs no special comment.

(*3*) It is interesting to note (59) that exposing to air at room temperature for a week a sample of CWSN 196 B1X that had been treated with nitrogen at 1000°C. and cooled in a stream of nitrogen restored the original complex to such an extent that the evolution of carbon dioxide on heating to 1200°C. was as large as with the original untreated sample, and that of carbon monoxide was two-thirds as large. Exposure of a heat-treated sample of this charcoal to oxygen at 300°C. for 30 min. put on more complex than was characteristic of the original charcoal, as shown in table 8; the carbon monoxide and carbon dioxide content was still, however, much smaller than that of some of the CWSN samples treated with oxygen at 400°C. by Young (153).

(*4*) A few experiments were carried out to compare the surface complex of charcoals aged at high relative humidity (24) for a considerable time with the complex of unaged samples. The oxygen content of the charcoals increased during aging in all cases by about 2 per cent in absolute value (33–100 per cent relative increase in oxygen). The increase in oxygen (13, 59) found by our degassing experiments on charcoals CWSN S5, CWSN 44, and PCI P58 was 2.12, 1.85, and 1.43 compared with values of 2.6, 2.3, and 1.2 found by ultimate analyses by Young (153). It should be noted that heating aged samples of CWSN S5 for 3 hr. at 115°C. produced no detectable change in composition or amounts of evolved gas.

(*5*) English workers (3, 4, 5, 7, 8, 9, 35, 107) have reported results which indicate that in the process of adsorbing vapors on charcoals, part of the surface complex is driven off into the gas phase. The displaced gases were reported to be equal in some cases to the equilibrium partial pressure of the adsorbate and to cause marked changes in the adsorptive characteristics of the charcoal. The actual volumes of displaced gas were not mentioned. To check this important factor, several experiments shown in table 9 were carried out (13, 59) on a charcoal made by the zinc chloride process and on a PCI sample made from coal.

TABLE 8

Effect of heat treatment on CWSN charcoals

SAMPLE	GAS EVOLVED, CC. (S.T.P.) PER GRAM														
	25–300°C.			300–600°C.				600–900°C.				900–1200°C.			
	CO	CO_2	H_2O	H_2	CO	CO_2	H_2O	H_2	CO	CO_2	H_2O	H_2	CO	CO_2	CH_4	H_2O
7. CWSN 196 B1X heated in nitrogen to 1000°C., cooled in nitrogen, and transferred in nitrogen	0.0	0.0	0.1	2.1	0.3	0.2	0.8	2.7	0.7	0.1	0.1	33.2	1.3	0.6	0.1	0.0
8. Same as No. 7 exposed to air for 1 week	0.3	3.5	3.9	1.2	1.5	5.6	2.6	4.5	6.0	0.3	0.1	33.2	1.2	0.7	0.3	0.1
11. CWSN 196 B1X exposed to oxygen at 300°C.	0.1	0.4	0.7	0.2	4.1	9.5	1.8	42.9	22.9	1.0	0.4	35.0	0.4	0.4	0.1	0.0

SAMPLE	TOTAL GAS EVOLVED, CC. (S.T.P.) PER GRAM									PER CENT BY WEIGHT EVOLVED		
	25–900°C.				25–1200°C.					H_2	O_2 (as CO, CO_2, and H_2O)	Weight per cent O_2 in ash
	H_2	CO	CO_2	H_2O	H_2	CO	CH_4†	CO_2	H_2O			
7. CWSN 196 B1X heated in nitrogen at 1000°C., cooled in nitrogen, and transferred in nitrogen	4.8	1.0	0.3	1.0	38.0	2.3	0.6	0.4	1.0	0.36	0.29	1.0*
8. Same as No. 7 exposed to air for 1 week	5.7	7.8	9.6	6.6	38.9	9.0	0.8	9.9	6.7	0.41	2.54	1.0*
11. CWSN 196 B1X exposed to oxygen at 300°C.	43.1	27.1	10.9	2.9	78.3	27.5	0.6	11.0	2.9	0.73	3.74	1.0*

* Ash assumed to be zinc oxide in computations of these values.

† See footnote to table 6.

The samples were evacuated at 120°C. before the run in each instance, at which temperature practically none of the carbon monoxide or carbon dioxide in the complex should be removed. The results clearly indicate that the amount of complex evolved by the adsorption of either carbon tetrachloride or chlorobenzene is very small, being equivalent in all cases to less than 0.01 per cent of the complex known to be present. Only water vapor displaced an appreciable amount of gas from the charcoals; the gas evolved by water was entirely carbon dioxide and was limited, for the most part, to the sample made by the zinc chloride process. It seems likely that most of this evolved carbon dioxide may have resulted from the attack on the zinc carbonate ash content by water condensed in capillaries. The total evolution of carbon dioxide in one case amounted to about 8 per cent of that which would have been evolved by heating the sample to 1200°C. The results as a whole fail to check the English work and certainly give no indication that physical adsorption of vapors is capable of seriously altering the composition of the surface complex on these typical charcoals.

(*6*) In view of the fact that most charcoals are activated by steam, it seemed worthwhile to ascertain the effect of steam activation on the surface complex. In table 10 the results are shown for such a series of experiments on charcoal CWSN 196 B1X after it had been extracted with hydrofluoric acid and heated 3 hr. in nitrogen at 1000°C. In general, the results obtained agree with those of Müller and Cobb (124), who studied the chemisorption of water vapor on an acid-extracted wood charcoal at temperatures ranging from 300°C. to 1100°C. Steaming at pressures up to and including 750°C. produced only a slight increase in the amount of adsorbed water and a total fixation of only 4.1 cc. of water vapor in a form evolved as carbon monoxide and carbon dioxide on heating. Over this temperature range, the hydrogen fixed was no greater than that calculated from the amount of oxygen fixed. The sample steamed at 900°C. to a 56 per cent weight loss clearly fixed more hydrogen than oxygen. This is in agreement with the experiments of Müller and Cobb (124), who noted more hydrogen than oxygen being fixed by steaming in the range 700–900°C. It does not agree with Ockrent's conclusion (128) that activated charcoal is covered with a layer of chemisorbed water. The total oxygen fixed at 900°C. was no greater than that on steaming at 750°C. In view of these results, it is easy to understand why the carbon monoxide and carbon dioxide complex is so low on samples of charcoal made by steaming at high temperature and not exposed excessively to air before cooling.

TABLE 9

Displacement of complex by adsorption of vapors at 25°C.

CHARCOAL	VAPOR	VOLUME OF LIQUID PER GRAM OF CHARCOAL	TIME OF ADSORPTION	GASES EVOLVED, CC. (S.T.P.) PER GRAM	
				CO	CO_2
		cc.	*hours*		
CWSN 196 B1	CCl_4	0.5	18	0.0028	0.0036
	C_6H_5Cl	0.4	5	0.00036	0.00039
	H_2O	0.4	4½	0.0014	0.495
	H_2O	0.2	2½	0.0024	0.205
	H_2O	0.1	16	0.0016	0.235
PCI P58	C_6H_5Cl	0.15	3	0.0016	0.00003
	H_2O	0.08	1	0.0025	0.0094

VII. SPECIAL SURFACE COATINGS ON CHARCOAL

There are statements in the literature (142) to indicate that the relative amount of different gases adsorbed may well depend upon the exact nature of

TABLE 10

Complex formed during steam activation

TEMPERATURE RANGE	GASES EVOLVED DURING DEGASSING, CC. (S.T.P.) PER GRAM OF CHARCOAL				
	H_2	CO	CH_4	CO_2	H_2O (vapor)
A. CWSN 196 B1X sample extracted with hydrofluoric acid and heated in nitrogen at 1000°C. for 3 hr.					
°C.					
25– 300	0.0	0.0	0.0	0.0	0.6
300– 600	0.3	0.0	0.0	0.1	0.2
600– 900	1.2	0.1	0.1	0.1	0.1
900–1200	14.2	0.2	0.3	0.4	0.0
Total.	15.7	0.3	0.4	0.6	0.9
B. Treated as in A, then exposed to water vapor at 300°C. for 3½ hr. (weight loss = 0.4 per cent)					
25– 300	0.0	0.0	0.0	0.1	0.8
300– 600	0.2	0.1	0.0	0.9	0.8
600– 900	1.1	0.6	0.1	0.2	0.1
900–1200	11.4	0.4	0.2	0.2	0.0
Total.	12.7	1.1	0.3	1.4	1.7
C. Treated as in A, then exposed to water vapor at 600°C. for 3½ hr. (weight loss = 1.0 per cent)					
25– 300	0.0	0.1	0.0	0.0	1.3
300– 600	0.1	0.0	0.0	0.3	0.6
600– 900	1.5	1.8	0.0	0.1	0.2
900–1200	12.3	2.3	0.2	0.3	0.1
Total......	13.9	4.2	0.2	0.7	2.2
D. Treated as in A, then exposed to water vapor at 750°C. for 1 hr. (weight loss = 1.6 per cent)					
25– 600	0.2	0.0	0.0	0.3	1.7
600– 900	2.7	2.3	0.1	0.3	0.4
900–1200	16.9	1.9	0.2	0.1	0.0
Total	19.8	4.2	0.3	0.7	2.1
E. Treated as in A, then exposed to water vapor at 900°C. for 3½ hr. (weight loss = 56 per cent)					
25– 300	0.0	0.0	0.0	0.4	0.6
300– 600	0.6	0.1	0.0	1.1	1.1
600– 900	5.8	1.3	0.2	0.2	0.2
900–1200	40.5	2.2	0.5	0.1	0.1
Total..	46.9	3.6	0.7	1.8	2.0

the surface coating of the charcoal. Because of the obvious importance of knowing the nature of any such changes that might be produced, a few experiments were carried out in an effort to coat charcoals with complexes other than carbon–oxygen complexes. Specifically, the influence of covering the surface with nitrogen, with chlorine, and with sulfur was investigated. The principal results obtained on samples with these coatings will now be considered.

A. Coating of charcoals with nitrogen

Literature references (22, 106) indicate that high-temperature treatment of charcoals with ammonia is capable of forming carbon–nitrogen complexes that are more stable than carbon–oxygen complexes. Accordingly, two sets of experiments were carried out (13, 59) in which an acid-extracted degassed sample of CWSN 196 B1X charcoal was heated in ammonia at 750°C. and at 900°C. The samples were then heated by Anderson to various temperatures up to 1200°C. and the evolved gases analyzed. The results, as shown in table 11, clearly confirm the previously published work. A nitrogen complex is formed that is evolved only on heating in the 900–1200°C. region. Most of the nitrogen comes off as free nitrogen, though some is evolved as hydrogen cyanide, cyanogen, and ammonia. It will also be noted that the hydrogen content of the charcoal is increased by the ammonia treatment from a value of 15.6 on the original sample to values of 30.5 and 39.3 cc. for the ammonia treatments at 750°C. and 900°C., respectively. Unfortunately, time did not permit further work with these ammonia-treated samples.

TABLE 11

Complex formed during ammonia activation of ash-extracted CWSN 196 B1X

TEMPERATURE RANGE	GASES EVOLVED DURING DEGASSING, CC. (S.T.P.) PER GRAM OF CHARCOAL					
	H_2	CO	N_2	C_2N_2 + HCN	NH_3	H_2O
A. Sample exposed to ammonia at 750°C. for 3 hr. (weight loss = 0.4 per cent)						
°C.						
25– 600	0.6	0.0	0.1	0.2	0.1	0.5
600– 900	3.3	0.1	0.2	0.1	0.1	0.5
900–1200	26.6	0.4	5.2	2.3	0.3	0.1
Total...........	30.5	0.5	5.5	2.6	0.5	1.1
B. Sample exposed to ammonia at 900°C. for 3 hr. (weight loss = 17.1 per cent)						
25– 300	0.0	0.0	0.0	0.0	0.0	0.6
300– 600	2.3	0.0	0.1	0.2	0.2	0.6
600– 900	5.2	0.1	0.1	0.2	0.2	0.3
900–1200	31.8	0.7	6.3	2.5	0.8	0.2
Total	39.3	0.8	6.5	2.9	1.2	1.7

B. Treatment of charcoals with chlorine

Chlorine complexes that are so stable (2) that the chlorine cannot be removed by evacuation (131) at temperatures as high as 600°C. or by the action of boiling 10 per cent sodium hydroxide over the period of an hour have been reported (135) in the literature. In the present work (59) charcoal has been made to retain as much as 17 per cent of its weight of chlorine even after evacuation for an extended period at 400°C. The results are shown in table 12 and in figure 32.

TABLE 12

Adsorption of chlorine by CWSN 196 B1X

TEMPERATURE OF EXPERIMENT USED IN ADSORPTION FLOW SYSTEM EMPLOYED	WEIGHT OF CHLORINE ADSORBED PER GRAM OF CHARCOAL AT VARIOUS TEMPERATURES				
	Physically adsorbed at 1 atm. and room temperature	Chemisorption retained after evacuation at			
		Room temperature	100°C.	200°C.	400°C.
Room temperature; flow experiment No. 1	0.626	0.252			
Room temperature; flow experiment No. 2.	0.719	0.202	0.081		
100°C.; flow experiment No. 3.	0.634	0.250	0.215	0.142	0.098
200°C.; flow experiment No. 4.	0.665	0.352	0.273	0.239	0.178
400°C.; flow experiment No. 5.	0.722	0.342	0.317		

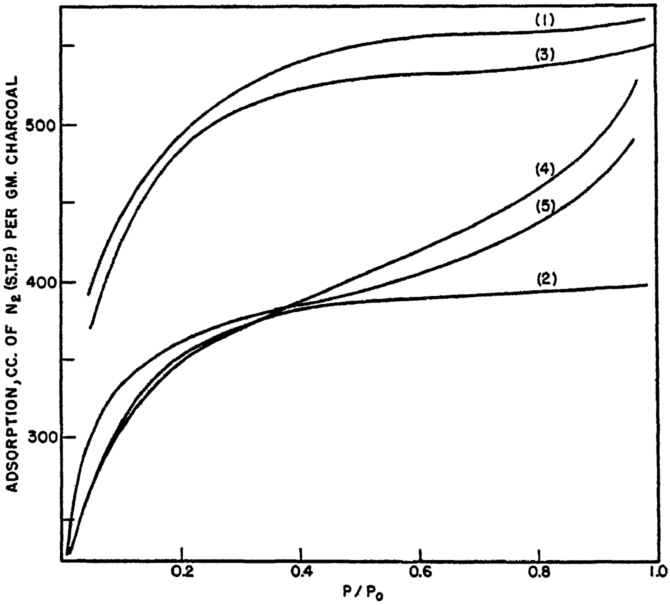


FIG. 32. Adsorption of nitrogen at −195°C. as a function of treatment of the charcoal with chlorine. (1) Untreated CWSN 196 B1X; (2) after chlorine adsorption at 200°C. and evacuation at room temperature; (3) after evacuation at 100°C.; and (4) and (5) after evacuation at 200°C.

The physical adsorption shown in column 2 is the amount that would pump off at room temperature after the sample was cooled from the temperature of the run to room temperature and was allowed to equilibrate with chlorine. Apparently the amount of stable chlorine held by the charcoal increases with the temperature of treatment. The amount retained at room temperature after evacuation is in general greater the higher the temperature of the original treatment, as is also the fraction of the total chemisorption that is retained on evacuation to 400°C.

Insufficient nitrogen-adsorption runs were carried out on the chlorinated sample to answer the question as to the location of the chemisorbed chlorine. In general, it may be said that the chemisorbed chlorine did not decrease the volume of nitrogen held by the charcoal at 0.99 as much as one would expect, though conclusions are uncertain until more runs are made. Figure 32 indicates clearly that on treating a sample at 200°C. with chlorine and then evacuating it at 200°C. a drastic change in pore size occurs. If these few experiments are to be believed, the change occurs during the long evacuation at 200°C. rather than during the original treatment, since evacuation at 100°C. left an isotherm similar to but 11 per cent smaller than the one for the untreated sample. The attack on the charcoal is not especially surprising, in view of the fact that one proposed method of producing active charcoal (144) involves burning hydrocarbons in chlorine under such conditions as to deposit a considerable portion of the hydrocarbon as free carbon.

C. Treatment of charcoals with sulfur

Young and his coworkers (154) prepared a number of samples of charcoal coated with sulfur by heating charcoal and sulfur together at 400°C. in a rotating furnace. Comparatively little work was done on the properties of the coated charcoals, though the following facts were established:

(*1*) As much as 41 per cent sulfur by weight could be incorporated into the charcoal. The amount of sulfur picked up was proportional to the amount included in the original mix.

(*2*) The 41 per cent sulfur content of one of the charcoals was reduced to 29 per cent by extraction with either of two different solvents. Apparently some of the sulfur is present in an extractable form and part of it in a more tightly bound form.

(*3*) The hydrogen content of the charcoal decreases to about a third of its orginal value as the sulfur content increases to 40 per cent.

(*4*) Water-adsorption isotherms show that if the sulfurized sample were protected from oxidation it picked up very little water below 0.5 relative pressure. The samples are definitely still hydrophobic. The sulfur, however, apparently decreases the pore volume of the charcoal considerably, as evidenced by the fact that the sample containing 41 per cent sulfur had only about 0.12 cc. of water sorptive capacity at saturation.

(*5*) There seems to be no relation between the acid and base adsorptive properties and the sulfur content.

VIII. RELATION BETWEEN ADSORPTION AND MOLECULAR STRUCTURE

In view of the fact that the efficiency of removal of war gases by gas mask charcoal is known to depend upon a rate factor and upon a capacity factor, N_0, it seemed worthwhile to carry out a study with a view to predicting the sorption capacity of a given charcoal for a gas at various relative pressures, as a function of the properties of that gas. It would be especially helpful to be able to predict approximately the shape of the adsorption isotherm of a gas on charcoal if only a few of the fundamental properties of the adsorbate gas are known. The analysis of the problem and the experimental results here presented are the work of Kummer (99); they give us a much better insight into the factors upon which the adsorbability of a gas depends than we have ever had before and enable us to predict with a fair approximation whether a gas will be adsorbed strongly, medium strongly, or weakly by a sample of charcoal.

All of the experimental measurements relative to this study were made on a single charcoal CWSN 19. It was one of the early samples of charcoal made by the zinc chloride process. It had an apparent density of 0.482, a particle density of 0.804, a carbon density (as determined by helium at 25°C.) of 2.09, an ash content of about 0.3 per cent (made up mostly of zinc oxide and zinc chloride), and a heat of wetting in benzene of 22.69 cal. per gram. As indicated in one of the earlier sections, the charcoal is characterized by a comparatively low amount of surface complex (59); on being heated to 1200°C. it evolved 57 cc. of hydrogen, 16.7 cc. of carbon monoxide, 2.7 cc. of methane, 3.3 cc. of carbon dioxide, and 2.1 cc. of water vapor, as is shown in table 7.

A. Experimental data for the adsorption of gases on CWSN 19

In figures 33 and 34 are shown the adsorption isotherms for a large number of gases. The data are plotted in the manner suggested by Goldman and Polanyi (73) as the fraction of the total sorption capacity taking place as a function of $RT \ln p_0/p$. A few regular isotherms plotted with relative pressure as the abscissa are given in figure 35. The adsorption data are summarized in table 13. It will be noted that the total liquid volume of gas adsorbed at saturation pressure is substantially constant and independent of the nature of the adsorbate (39). We shall now turn to the theoretical part of this work and summarize Kummer's derivation of relationships (99) that will enable one to predict the general nature of the adsorption of any adsorbate from its physical properties and the behavior of some other one adsorbate on the same charcoal.

B. Theory

In deriving a relation between the structure and adsorbability of a molecule, a number of equations were used. The Polanyi (73) relationship

$$T_1 \log p_1/p_{0_1} = T_2 \log p_2/p_{0_2} \qquad (16)$$

was employed to account for the dependence on temperature of adsorption of a given adsorbate where T_1 and T_2 are the two different temperatures of the adsorptions, p_1 and p_2 are the isotherm pressures corresponding to some definite amount of adsorption, and p_{0_1} and p_{0_2} are the vapor pressures of the liquid adsorbate at the two temperatures.

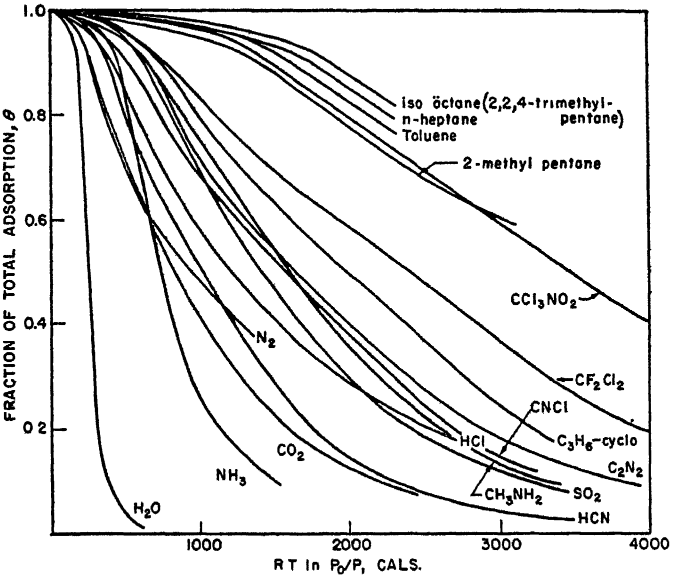


FIG. 33. Physical adsorption of gases on CWSN 19, plotted as the fraction θ of the adsorption at a given relative pressure compared to that at $p/p_0 = 0.99$ *vs.* $RT \ln p_0/p$.

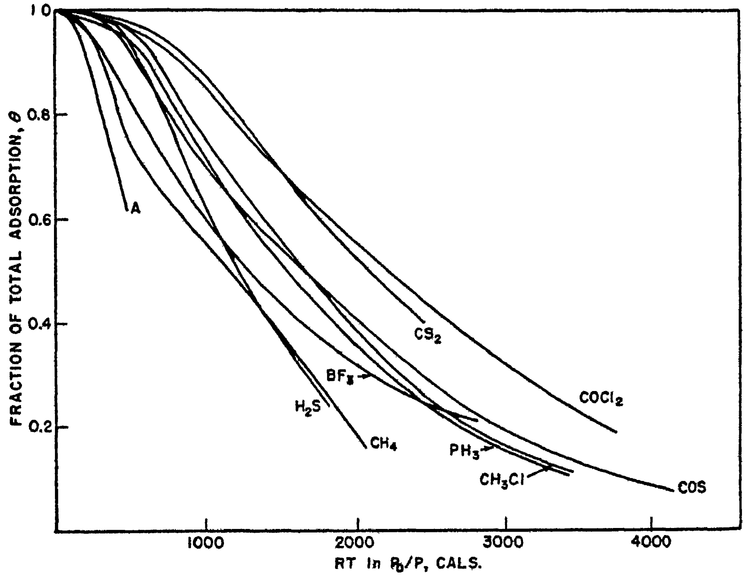


FIG. 34. Physical adsorption of gases on CWSN 19, plotted as in figure 33

The amount of adsorption as a function of the pressure of the adsorbate was, for convenience, expressed in terms of the empirical equation

$$-RT \ln p/p_0 = K(1 - \theta)^{1/3} - B \ln \theta \qquad (17)$$

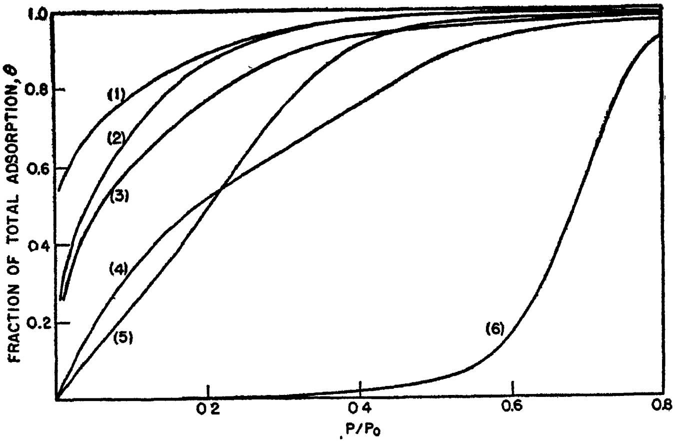


FIG. 35. Isotherms of a variety of gases on CWSN 19 plotted as the fraction, θ, of the maximum adsorption against relative pressure. Curve 1, nitrogen at −195°C.; curve 2, hydrogen sulfide at −78°C.; curve 3, cyanogen chloride at 0°C.; curve 4, hydrogen cyanide at 25°C.; curve 5, ammonia at −46°C.; curve 6, water at 25°C.

TABLE 13

Adsorption data for various gases on CWSN 19

GAS	TEMPERATURE OF ADSORPTION	ADSORPTION AT A RELATIVE PRESSURE OF 0.99; CC. OF GAS (S.T.P.) PER GRAM OF CHARCOAL	ADSORPTION AT A RELATIVE PRESSURE OF 0.99; CC. OF LIQUID ADSORBATE PER GRAM OF CHARCOAL
	°C.		
N_2	−194	397	0.616
A	−194	490	0.600
CH_4	−160	360	0.610
BF_3	−78	291	0.600
PH_3	−78	298	0.615
HCl	−78	442	0.613
CO_2	−78	355	0.554*
H_2S	−78	371	0.566
CF_2Cl_2	−20	166	0.609
NH_3	−46	526	0.572
COS	−46	262	0.608
CH_3Cl	−20	264	0.600
C_2N_2	−21	245	0.595
Cyclopropane	−39	216	0.590
CH_3NH_2	0	296	0.596
SO_2	0	298	0.595
$COCl_2$	0	193	0.596
CNCl	0	267	0.598
HCN	25	350	0.607
CS_2	25	216	0.585
H_2O	40	644	0.520
n-Heptane	25	87	0.567
Toluene	25	120	0.574
CCl_3NO_2	25	128	0.570
2-Methylpentane	25	95	0.560
Isoöctane (2,2,4-trimethylpentane)	25	76	0.563

* Liquid density.

where θ represents the fraction of the saturation value of the adsorption that is occurring at pressure p, and K and B are constants. The relation was found to hold fairly well for all adsorbates on CWSN 19. It gives an isotherm in which the slope dV/dP decreases continuously as the pressure increases and equals zero when $p = p_0$. For those charcoals which give an S-shaped isotherm equation 17 would not hold above $p/p_0 = \sim 0.5$. However, since a gas mask is rarely called upon to afford protection from gases which have attained a partial pressure in the air equal to one-half the vapor pressure of the liquid adsorbate, equation 17 will be used even though it is inapplicable above a relative pressure of 0.5.

If constants K and B could be evaluated from molecular data for the adsorbate, the given problem would be completely solved. It is extremely difficult to do this with exactness. Accordingly, a somewhat simpler but useful approach to the problem was made by outlining a method for calculating the difference between the integral heat of adsorption, $-\Delta H_I$, and the heat of liquefaction, $-\Delta H_L$, for the adsorbate on the basis of the fundamental properties of the adsorbate molecule. Since it was well established that at a given temperature adsorption isotherms follow curves of A, B, or C type shown in figure 36, depending upon whether the heat of adsorption is greater than, equal to, or less than the heat of liquefaction, it would obviously then be possible with the help of the calculated value of $(\Delta H_I - \Delta H_L)$ to indicate the general nature of adsorption.

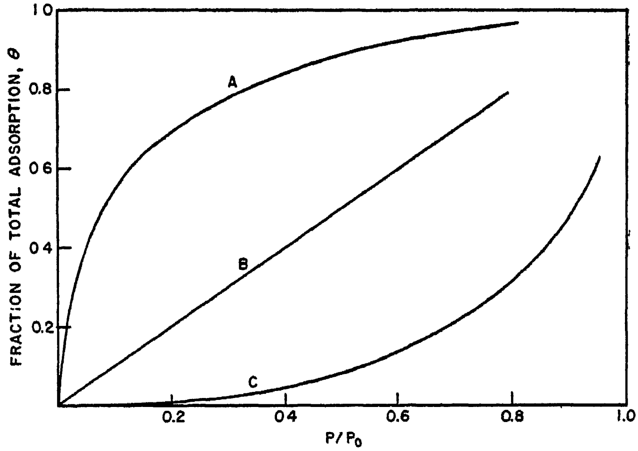


FIG. 36. Shape of hypothetical isotherms as a function of the heat of adsorption at a given temperature. Curves A, B, and C correspond respectively to heat of adsorption greater than, equal to, or less than the heat of liquefaction.

In obtaining a solution to the problem, the thermodynamic equation

$$-RT \ln p_0/p = + \left(\frac{\partial(\Delta H_a)}{\partial n}\right)_T - \Delta H_L - T\left(\frac{\partial \Delta S}{\partial n}\right)_T \tag{18}$$

for the transfer of a mole of absorbate from bulk liquid to an adsorbed form at pressure p on a solid was set up to relate the relative pressure p/p_0 of the adsorption to $\partial(\Delta H_a)/\partial n$, the differential molal enthalpy of adsorption for the gas going to the adsorbed phase, to ΔH_L, the molal change in heat content during condensation of gaseous adsorbate to bulk liquid, and to $\partial(\Delta S)/\partial n$, the differential molal entropy change when the bulk liquid is transferred to the surface layer.

If equation 16 holds, it can be shown that the entropy term disappears and that

$$-RT \ln p_0/p = \frac{\partial(\Delta H_a)}{\partial n} - \Delta H_L \tag{19}$$

Coolidge's data (38) show that many of the organic gases follow equation 16 very closely, whereas water does not.

In order to estimate the entropy term, some assumptions were necessary. For one thing, it was necessary to assume some shape factor for the capillaries in order to be able to know the fraction of liquid adsorbate in contact with the surface of the charcoal. Kummer pointed out that the exact form of the assumption is not too important, because with a variety of choices the final calculated difference between the integral heat of adsorption and the heat of liquefaction does not change much. For simplicity, it was assumed that the charcoal pores had plane parallel walls four molecular diameters apart. The entropy term is usually written in the form $RT \ln \phi/1 - \phi$, where ϕ represents the fraction of the surface covered by adsorption. However, it appeared simpler for physical adsorption to assume that the rate of condensation on the surface is proportional to the total surface rather than to $1 - \phi$; hence, the entropy term was written

$$\frac{\partial(\Delta S)}{\partial n} = -R \ln \phi \tag{20}$$

This expression is assumed to hold for all values of ϕ less than 1. For ϕ greater than 1 the entropy term becomes zero, since rate of evaporation and condensation both are constant and independent of ϕ. If, as is likely, most of the first layer will form before the second begins, then $\phi = 2\theta$.

Combining equations 17, 18, and 20 gives

$$-\partial\left(\frac{\Delta H_a}{\partial n}\right)_T + \Delta H_L = K(1 - \theta)^{1/3} - B \ln \theta + RT \ln 2\theta \tag{21}$$

The integral heat of adsorption was found by integrating the entire expression including the last term from $\theta = 0$ to $\theta = 0.5$; and, without the last term, from 0.5 to 1. The integral heat of adsorption, $-\Delta H_I$, obtained in this way was:

$$-\Delta H_I = -\Delta H_L + 3/4K + B - 1/2RT = -\Delta H_L - \Delta H_x \tag{22}$$

The integral heat of adsorption up to complete filling of the pores was used, because complete filling represents a definite physical state which is the same for all gases and which lends itself to theoretical calculations.

In order to calculate the integral heat at saturation, the following simple process was visualized: (*1*) One mole of gas was condensed into a bulk liquid, the enthalpy change being by definition ΔH_L. (*2*) Next, this bulk liquid was spread out into a sheet four molecules thick. The enthalpy change for this step would be one-half the enthalpy change on bringing a mole of adsorbate from the interior or bulk liquid to the surface of the liquid, or $\Delta H_s/2$. (*3*) Both sides of this sheet were allowed to come in contact with a charcoal surface, giving an enthalpy change of $\Delta H_c/2$, where $-\Delta H_c$ is the heat that would be evolved if all of the molecules in the mole of adsorbate were brought as a sheet of liquid into contact with the carbon surface. Then

$$\Delta H_I = \Delta H_L + \Delta H_c/2 + \Delta H_s/2 \tag{23}$$

Next, a means was sought and found for evaluating ΔH_c and ΔH_s that depends upon the physical properties of the adsorbate molecule. The enthalpy change when a molecule is brought from the interior of a liquid to the surface is largely independent of the temperature and can be calculated by

$$\Delta H_s = +2.22k_e(T_c - 6) \tag{24}$$

where k_e is Eötvös' constant and T_c is the critical temperature. One, therefore, has a ready means of calculating $\Delta H_s/2$, the heat required to form a mole of liquid into a sheet four molecules thick, provided T_c and k_e are known. If k_e is not known, it may be taken as about 2 for most substances.

The heat quantity ΔH_c was evaluated by means of the theory of London (99, 111) and was shown by him to be given by the expression

$$-\Delta H_c = \frac{3N\alpha_c\alpha_g 2V_{0c}V_{0g}}{4h^3(V_{0c} + V_{0g})} \tag{25}$$

where α_c is the polarizability of the carbon surface, α_g is the polarizability of the gas molecules, V_{0c} is the fundamental frequency of the carbon surface, V_{0g} is the fundamental frequency of the gas molecules, N is the number of atoms per cubic centimeter of adsorbent, and h is the distance between the carbon surface and the molecules of adsorbate when the sheet is at its equilibrium position. As a first approximation[8] $3N\alpha_c V_{0c}/2h^3(V_{0c} + V_{0g})$ may be taken as a constant C_1 and the equation simplified to:

$$-\Delta H_c = C_1\alpha_g V_{0g} \tag{26}$$

C_1 was evaluated from some one adsorbate and then was assumed to be constant for other adsorbates. Substituting expressions 23, 24, and 26 in equation 22 led to the equation

$$\tfrac{1}{2}[C_1\alpha_g V_{og} - 2.2k_e(T_c - 6)] = \tfrac{3}{4}K + B - \tfrac{1}{2}RT = -\Delta H_x \tag{27}$$

This equation when rearranged became

$$C_1\frac{\alpha_g}{2}V_{0g} = -\Delta H_x + 1.11(T_c - 6)k_e = -\Delta H_x + \tfrac{1}{2}\Delta H_s \tag{28}$$

---

[8] The approximate nature of this assumption is evident when one realizes that if h is taken as the sum of the van der Waals radius for carbon and for the adsorbate molecule, it will vary from 3.44 to 4.28 for the adsorbates shown in table 15, and $V_{0c} + V_{0g}$ will vary from 447 to 694. Nevertheless, since α_g varies from 1.48 to 10.8 and V_{0g} from 188 to 435, this approximation will not result in large discrepancies. A refined procedure that introduces values for h for the different adsorbates is now being submitted for publication by Kummer.

TABLE 14

Fundamental data on the adsorbate gases

GAS	MOLECULAR WEIGHT	DENSITY	TEMPERATURE	$-\Delta H_L$	MOLAL VOLUME	AVERAGE RADIUS CALCULATED FROM LIQUID DENSITY	DIPOLE MOMENT $\mu \times 10^{18}$	POLARIZIBILITY, α_g	FUNDAMENTAL FREQUENCY, V_0	ISOTHERM CONSTANTS		TOTAL SURFACE ENERGY, ΔH_s	$-\Delta H_x$	$\alpha_g V_{0g}$	$-\Delta H_x + 1/2\Delta H_s$
										K	B				
		g./cc.	°C.	cal./mole	cc.	Å.	debyes	cc. × 10^{24}	kg.-cal.			cal /mole	cal./mole		cal./mole
N_2	28.02	0.805	−194	1335	34.9	2.16	0.0	1.74	402			561		700	
A	39.94	1.454	−194	1590	27.4	2.00	0.0	1.63	396			643		645	
CH_4	16.04	0.422	−160	2040	38.0	2.23	0.0	2.54	324	240	1210	817	1268	822	1677
BF_3	67.82	1.47	−78	4620	43.0	2.32	0.0	2.40	435	295	1555	1460	1581	1043	2311
PH_3	34.04	0.736	−78	3489	46.3	2.37	0.55	3.50	(300)	650	1485	1410	1778	1050	2483
HCl	36.46	1.174	−78	3860	31.1	2.08	1.03	2.63	311	394	1300		1401	818	
CO_2	44.01	1.26 (liq.)	−78	4130	34.9	2.16	0.0	2.57	357	292	816	1320	8840	916	1500
H_2S	34.08	0.993	−78	4463	34.3	2.15	1.10	3 64	257	1060	608		1208	935	
COS	60.07	1.154	−46	4423	52.0	2.47	0.65	5.05	313	765	1417	1740	1741	1580	2620
C_3H_6	42.05	0.688	−39		61.1	2.61	0.0	4.45	307	1170	1451		2061	1675	
NH_3	17.03	0.697	−46	5720	24.4	1.92	1.49	2.14	271			1290		580	
CH_3Cl	50.5	0.99	−20	5170	51.0	2.45	1.86	4.41	312	1117	1081	1910	1667	1380	2622
C_2N_2	52.02	0.953	−21	5576	54.6	2.51	0.0	4.65	285	870	1290	1840	1689	1322	2609
SO_2	64.06	1.432	0	5960	44.7	2.35	1.67	3.76	272	1020	915	2050	1407	1022	2432
$COCl_2$	98.92	1.428	0	5990	69.3	2.72		6.51	274	1735	1409	2100	2256	1785	3306
CNCl	61.48	1.226	0	6300	50.1	2.44		4.58	(300)	938	1150		1581	1372	
HCN	27.02	0.695	25	6027	38.9	2.24	2.6	2.46	321	552	765	1100	881	790	1431
CS_2	76.13	1.256	25	6490	60.6	2.60	0.0	8.03	188	1610	1192	2520	2102	1510	3362
n-Heptane	100.2	0.684	25	7650	146.1	3.49	0.0	13.7				2490			
H_2O	18.02	0.995	40	10400	18.1	1.74	1.85	1.48	311	360	10	1520	0	460	760
Toluene	92.13	0.862	25	7980	107.0	3.14	0.4	12.3				2870			
CH_3NH_2	31.06	0.687	0		45.2	2.36	0.99	3.88	294	1110	990	1145	1549	1140	2121
2-Methylpentane	86.1	0.654	25	7000	132.0	3.37		11.8							
Isoöctane	114.1	0.692	25	8200	165.0	3.63		15.5							
CCl_3NO_2	164.4	1.641	25		100.0	3.08		10.82	(280)	2620	2000	3640	3667	3030	5487
CF_2Cl_2	120.9	1.47	−20	4760	82.1	2.88		6.55	(300)	1160	1910	1850	2530	1970	3455

Table 14 shows values of K, B, and ΔH_x as calculated by Kummer from the isotherms, together with ΔH_s and physical data for the various adsorbate molecules. Figure 37 is a plot of $\alpha_g V_{0g}$ against $-\Delta H_x + 1/2\Delta H_s$. The value of C_1 turns out to be 3.75 and is equal to twice the slope of the plot.

As pointed out above, complete solution of the problem requires a method for evaluating the absolute values of K and B. This has not yet been accomplished. However, at the present stage of development as pointed out by Kummer (99), it is possible to evaluate $\Delta H_I - \Delta H_L$ for any adsorbate from the experimental adsorption values for some standard adsorbate at a given temperature on a charcoal, together with fundamental data for the standard adsorbate and for the adsorbate for which $\Delta H_I - \Delta H_L$ is sought. For the standard adsorbate one can calculate K and B for the given charcoal from an isotherm. From equation 27 and values for T_c, for the Eötvös constant, for the polarizability of the standard molecule, and for its fundamental frequency one can then obtain a value for the constant C_1.[9] For other adsorbates then on the same charcoal, one has merely to insert values for α_g and V_{0g} in equation 26, and obtain a value for ΔH_c. Knowing ΔH_s from the Eötvös equation, one can then calculate ΔH_x and hence by equation 23 obtain a value for $\Delta H_I - \Delta H_L$. In other words, by knowing a single adsorption isotherm of any one adsorbate on a given charcoal and by knowing the polarizability, critical temperature, Eötvös constant, and fundamental frequency of the molecules of the adsorbate whose adsorption one wishes to evaluate, and

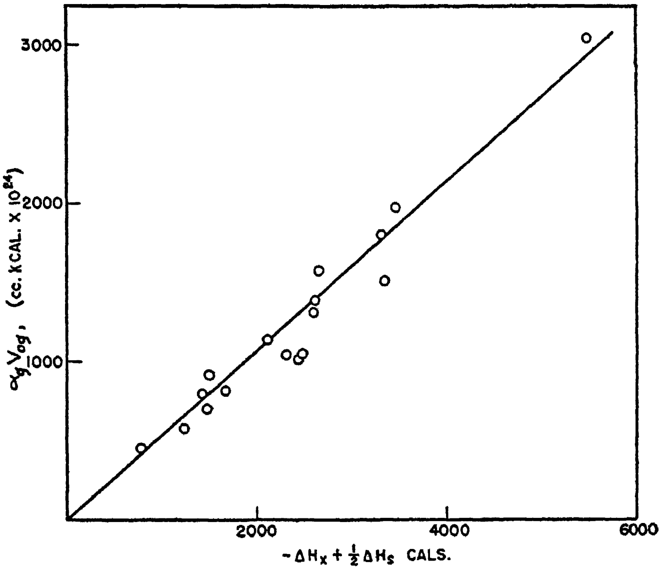


FIG. 37. Evaluation of the constant C_1 of equation 28 by plotting $\alpha_g V_{0g}$ against $-\Delta H_x + 1/2\Delta H_s$.

---

[9] The value of α_g can be readily calculated by the method of Denbigh (44) from the structure of the molecule. The value of V_{0g} for organic molecules lies (111) within ± 20 per cent of the value 286 kg.-cal. per mole.

of the standard adsorbate, one is able to tell whether the difference between the integral heat of adsorption and the heat of liquefaction is a large positive quantity, a small positive quantity, or zero.

To show the usefulness of this method of procedure, there are listed in table 15 values for $-(\Delta H_I - \Delta H_L)$ for the various adsorbates as determined experimentally and as calculated using the isotherm for chloromethane for evaluating the constant C_1. It is readily apparent that one would not be misled as to the nature of the adsorption isotherm of any of the gases listed by the calculated value for the difference between the integral heat of adsorption and the heat of liquefaction of the adsorbate.

TABLE 15

Calculation of $-(\Delta H_I - \Delta H_L)$ *for various adsorbates on CWSN 19, assuming adsorbate is in capillaries with parallel walls four molecular diameters apart*

Heat values are in calories per mole

GAS	TEMPERATURE OF ADSORPTION	$-(\Delta H_I - \Delta H_L)$ FROM ACTUAL ISOTHERMS BY EQUATION 22	$-(\Delta H_I - \Delta H_L)$ CALCULATED FROM CONSTANT C_1 FOR CH_3Cl AND VALUES FOR $\alpha_g V_{0g}$ AND ΔH_s	$\frac{\text{COLUMN 4*}}{T\ (^\circ\text{K.})}$
	°C.			*cal./mole degree*
CH_4	−160	1269	1131	10.0
BF_3	−78	1589	1230	6.3
PH_3	−78	1778	1255	6.4
CO_2	−78	840	1050	5.4
COS	−46	1750	2080	9.2
CH_3Cl	−20	1667	1667	6.4
C_2N_2	−21	1689	1560	6.2
SO_2	0	1407	895	3.3
$COCl_2$	0	2256	2290	8.4
HCN	25	881	925	3.1
CS_2	25	2102	1570	5.3
CH_3NH_2	0	1549	1568	5.9
CCl_3NO_2	25	3667	3860	13.0
CF_2Cl_2	−20	2530	2755	10.9
H_2O	40	0	−23	<1.0

* The temperature used in calculating this column is the absolute temperature at which the isotherm for each gas was determined.

The question naturally arises as to the extent to which the results in table 15 are dependent upon the nature of the assumption made as to the shape of the pores in the capillary. If one assumes that the adsorption is taking place in pores that are cylindrical and four molecules in diameter, one obtains an equation similar to 21, except that the constant 2 is changed to about 1.5. Values for $-(\Delta H_I - \Delta H_L)$ as calculated for this postulate by the proper modification of equations 23, 26, 27, and 28 are shown in table 16; it is evident that to a close approximation one can estimate the magnitude of the difference between the heat of adsorption and the heat of liquefaction without too much error being entailed by the nature of the assumption that has to be made relative to the shape of the pores of the charcoal. The procedure here presented should, therefore, be very useful in quickly evaluating the probable adsorption characteristics of any adsorbate if the polarizability, the fundamental frequency, and surface energy of the adsorbate molecule are known. It has been stated above that in a qualitative sense, as illustrated in figure 36, gases will be strongly, weakly, or very weakly adsorbed depending on whether the heat of adsorption is greater than, equal to, or less than the heat of liquefaction. However, strictly speaking, it is the constant C in equation 3 that is important in fixing the extent of adsorption of an adsorbate at a definite, relative pressure on a given adsorbent. C, as defined in equation 2, is proportional to $e^{(E_1-E_L)/RT}$. Hence, both the energy of adsorption and the temperature must be taken into consideration. Furthermore, $E_1 - E_L$ is not exactly the same as $-(\Delta H_I - \Delta H_L)$, because the $-\Delta H_I$ is the integral heat of adsorption all the way to a relative pressure of 1, whereas E_1 is the average heat of adsorption for the first layer. Nevertheless, for an adsorbent such as charcoal, which has such narrow pores as to permit only a few layers to be adsorbed, there should not be much error involved in using $-(\Delta H_I - \Delta H_L)$ in place of $E_1 - E_L$ in equation 3. It follows, then, that $-(\Delta H_I - \Delta H_L)/T$ should be used in estimating the extent to which a given adsorbate will be taken up by charcoal. To facilitate such a comparison the calculated $-(\Delta H_I - \Delta H_L)/T$ values for the various gases are shown in column 5

TABLE 16

Calculation of $-(\Delta H_I - \Delta H_L)$ for various adsorbates on CWSN 19, assuming adsorbate is in cylinders four molecules in diameter

Heat values are in calories per mole

GAS	TEMPERATURE OF ADSORPTION	$-(\Delta H_I - \Delta H_L)$ FROM ACTUAL ISOTHERM DATA	$-(\Delta H_I - \Delta H_L)$ CALCULATED FROM CONSTANT C_1 FOR CH_3Cl AND VALUES FOR $\alpha_g V_{0g}$ AND ΔH_s	$\frac{\text{COLUMN 4*}}{T\ (°K.)}$
	°C.			cal./mole degree
CH_4	−160	1232	1155	10.2
BF_3	−78	1524	1185	6.1
PH_3	−78	1713	1230	6.3
CO_2	−78	775	1020	5.3
COS	−46	1684	2110	9.3
CH_3Cl	−20	1584	1584	6.2
C_2N_2	−21	1606	1514	6.0
SO_2	0	1316	760	2.8
$COCl_2$	0	2165	2290	8.4
HCN	25	781	965	3.2
CS_2	25	2002	1440	4.8
CH_3NH_2	0	1459	1582	5.8
CCl_3NO_2	25	3567	3854	12.9
CF_2Cl_2	−20	2457	2438	9.6
H_2O	40	−113	−64	<1

* The temperature used in calculating this column is the absolute temperature at which the isotherm for each gas was determined.

of tables 15 and 16. The higher the value of the ratio, the stronger the adsorption at the temperature, T, of column 2. Thus, at about room temperature, water vapor would be least strongly, and chloropicrin most strongly adsorbed.

If one wishes to estimate the amount of adsorption at room temperature rather than at the temperature T of column 2 of tables 15 and 16, one should make use of equation 3. V_m of the adsorbate for which one wishes to estimate an adsorption value can be obtained by noting the V_m value for the standard adsorbate and multiplying this latter value by the ratio of the molecular cross-sectional area of the standard molecule to that of the adsorbate being studied. By inserting the value of V_m, C (taken as $e^{-(\Delta H_I - \Delta H_L)/RT}$, and n (as estimated from the standard adsorbate) into equation 3, one can calcuate the adsorption for the desired adsorbate at relative pressure x. Since actual adsorption usually deviates at low relative pressure in the direction of being greater than that estimated from equation 3, the method here outlined for estimating the adsorbability of a substance present in low concentrations is conservative and would give adsorption values which, if in error at all, would be likely to be too low.

Volman and Klotz (157) have contributed one of the few helpful suggestions for explaining why some adsorbates such as water vapor are not strongly adsorbed by charcoal. They point out that molecules of water, methanol, ethanol, ammonia, and a few other substances are strongly hydrogen bonded in the liquid phase. Were it not for such hydrogen bonding water would presumably boil at −80° to −100°C. and might have a vapor pressure of the order of 20,000 mm. of mercury at room temperature. Consequently, they conclude that at a relative pressure of, say, 0.3, water behaves in adsorption not involving hydrogen bonding as though it were an adsorbate at 0.0003 relative pressure and therefore is only slightly adsorbed. Only at higher relative pressures where water molecules have a chance to form hydrogen bonds with each other in the adsorbed phase does the adsorption increase rapidly with pressure.

Apparently Kummer's calculations take these facts into consideration by using the actual properties of the liquid phase including the Eötvös constant, critical temperature, and boiling point in calculating the probable behavior of an adsorbate. His calculations, however, do not explicitly call attention to the hydrogen-bonding explanation.

In concluding this section, it may be well to emphasize the type of information that is furnished by the theoretical considerations of Kummer and of Volman and Klotz. As discussed above, Kummer's calculations enable one to predict whether an adsorbate is going to be slightly, medium strongly, or strongly adsorbed on a particular sample of charcoal for which one has an adsorption isotherm of some standard adsorbate. For example, it enables one to predict that the water isotherm (curve 6, figure 35) will resemble curve C, figure 36, in showing very slight adsorption; that hydrogen cyanide (curve 4, figure 35) will be medium strongly adsorbed and will resemble curve B, figure 36; and that chloropicrin will be strongly adsorbed and will resemble curve A, figure 36. Thus, even though his calculations involve integral heats of adsorption, they do assign the isotherms to general adsorption types and thereby give information as to the adsorption at low relative pressures as well as at higher relative pressures. Volman and Klotz's suggestion enables one to predict that for any molecules tending to form hydrogen bonds in the liquid phase, adsorption on an adsorbent with which hydrogen bonds will not be formed will be smaller than one would expect. Accordingly, with the help of the ideas advanced by Kummer and those proposed by Volman and Klotz, it is now possible to predict, much more accurately than formerly, the possible behavior of a given adsorbate on a sample of charcoal, even though the adsorbate is present in amounts corresponding to a low relative pressure.

IX. RETENTIVITY OF CHARCOALS

Allmand (6, 10) and his coworkers showed many years ago that it is possible to use a retentivity method for determining approximate adsorption isotherms for a vapor on a solid adsorbent. Thus, by saturating a sample of charcoal with given partial pressures of vapors and then noting the change in concentration of the effluent gas when vapor-free air is passed into the sample, an approximate adsorption isotherm can be constructed which would give the amount of adsorbate left on the sample as a function of the exit partial pressure of the adsorbate. Ordinarily, the approximate isotherms so obtained will be somewhat lower than a true isotherm, because the charge left on the charcoal at any stage in the desorption is not uniformly distributed but is concentrated more at the exit than the entrance to the bed of adsorbent. Nevertheless, such approximate isotherms serve as a useful means of predicting the initial exit concentration of vapor that one could expect from a bed of charcoal as a function of the amount of adsorbate that has been taken up and has been permitted to become redistributed throughout the charcoal. This technique also permits one to determine the influence of moisture on the retentivity.

During the war Volman, Doyle, and Blacet (145) have obtained some interesting retentivity results for a number of organic vapors as a function of the moisture content of the charcoal and gas stream. Approximate isotherms were constructed by the retentivity method for carbon tetrachloride, chloroform, carbon disulfide, ethylene dichloride, methyl ethyl ether, neopentane, acetone, and methanol (145). It was concluded that water vapor decreased the amount of adsorbate that could be held at equilibrium and decreased the retentivity very markedly for all vapors that were insoluble in water. For those that were slightly soluble the effect was less pronounced, and for those that are miscible in all proportions with water, no appreciable decrease in the total sorption capacity or retentivity of the charcoal was found to occur. As a matter of fact, for methanol it was shown that the isotherm in the presence of water could be derived from the dry isotherm and the water isotherm. These results seem to be consistent with similar work that has already been published, including the influence of water vapor on the adsorption of chloropicrin (108).

X. CHEMISORPTION ON THE CUPRIC OXIDE IN TYPE A WHETLERITES

In order to obtain some idea as to the extent of surface of the inorganic material added to base charcoals in the course of making type A whetlerites, a search was made for a gas that would not be strongly adsorbed on charcoal and that would form only a layer of chemically bound adsorbate on the cupric oxide attached to the charcoal. At the same time, measurements were made on two different samples of cupric oxide of known surface areas.

The detailed results of the work need not be given here (67). It will suffice to point out that hydrogen sulfide, phosphine, cyanogen chloride, boron trifluoride, hydrogen chloride, acetylene, and nitric oxide all appear to react at room temperature with the cupric oxide in type A whetlerites to a depth in excess of a monolayer and hence will not serve for measuring the surface area of the whetlerizing ingredients. Hydrogen sulfide, cyanogen chloride, boron trifluoride, and hydrogen chloride seem especially reactive and probably combine almost stoichiometrically with the copper oxides present. Nitric oxide reacts extensively even with the base charcoal.

Carbon monoxide, sulfur dioxide, water, cyanogen, and ammonia are all chemisorbed in amounts that do not exceed a monolayer. The results obtained with these gases indicate that on the three type A whetlerites investigated, about 3 cc. of gas is required to form a monolayer on the copper oxides of the whetlerite. This corresponds to a particle size of about 100 Å. for the cupric oxide crystals.

XI. THE STRUCTURE OF CHARCOAL

There are very few things about which we can be sure as regards the structure of charcoal. Perhaps one of the few things we can say with confidence is that an active adsorptive charcoal must contain a network of capillaries, some large and some small. This seems essential in order to provide avenues by which the molecules that are to be adsorbed can gain entrance to the interior of the charcoal particles and to the large surface area that must necessarily be located in small pores. When, however, we come to a discussion of the pore shape and ask whether we should consider charcoal as a honeycomb structure of approximately cylindrical pores, or as a collection of platelets more or less parallel to each other and forming box-like capillaries of rectangular cross section, or some combination of these, or some arrangement involving pores of still different shapes, we find ourselves in the realm of speculation and are unable to speak with certainty. Perhaps the best procedure to follow in summarizing the evidence is to consider the results obtained from each of the principal tools and types of measurement from which we can hope to obtain information as to the pore shape and the general structure of charcoal. These various approaches will include x-ray diffraction studies, microscopic studies, electron microscope studies, measurements and calculations of area and pore volume, chemical behavior of charcoal, expansion of charcoal during adsorption, and measurements of the true density of the carbon in charcoal. These will now be discussed in turn.

A. X-ray structure work on charcoal

In an extended series of papers Johnstone and Clark (84, 86) have reported the results of their study of the structural characteristics of some 1200 samples of carbons, cokes, activated charcoals, resins, and gas mask adsorbents of all kinds. A number of their observations relating to the charcoals are as follows: (*1*) Charcoals sinter and turn into graphite much less readily than does petroleum coke. (*2*) The value of *c* (twice the spacing between planes in the *c* direction) is about 7.72 Å. for a coconut charcoal and 7.47 Å. for a charcoal made by the zinc chloride process, provided the samples have not been heated over 1100°C. This compares with 6.70 Å. for graphite. (*3*) These charcoals appear to contain a number of platelets which in the *c* direction are about 10 Å. in thickness; for a few other charcoals this thickness is as high as 12 Å. This is in good agreement with the work of Berl (23) and of Hofmann and Sinkel (82). The discs or platelets of carbon revealed by the x-ray studies are broader than they are thick. For coconut charcoal they range in width from about 20 Å. for samples that have been heated to no more than 500°C., to 39 Å. for samples that have been heated to 1000°C. Values for this L_a dimension for zinc chloride charcoals start at 20 Å. as for the coconut charcoal, but extend up to 45 Å. for samples heated to 900°C. and to 63 Å. for samples heated to 1100°C.

The x-ray results taken as a whole constitute strong evidence that much of the carbon in charcoal is arranged in platelets. The preferential growth of these in one direction seems to be especially convincing evidence of their reality. Johnstone and Clark conclude (84) that "the data obtained from the x-ray study evidently give credence to the idea that activation is essentially a process of cleaning out capillaries, in changing their size and perhaps their shape, without greatly affecting the matrix structure of carbon."

B. Microscopic studies

During the recent war no extensive microscopic studies of charcoals were reported. However, it is well known from published reports (71, 100) that it is possible to show up by photomicrographs the presence of large capillaries in the surface of charcoal particles. Necessarily, the limit to such studies is about 0.5 micron, so that capillaries smaller than about 5000 Å. will not be observable. These microscopic studies, accordingly, will merely confirm the presence of the large connecting channels by which the gases that are to be adsorbed gain access to the interior of the particles. They show nothing about the shape or distribution of the fine pores.

C. Electron microscope studies

Electron microscope pictures push the microscopic observations out to capillaries smaller by perhaps a factor of 50 than those observable in the ordinary light microscope. The results have been well expressed in a summary of the report by Johnstone, Clark, and Le Tourneau (87): "Thirty-six electromicrographs of various charcoals are presented. While they do not reveal the ultimate pore structure of the charcoal, they do show a pore structure in the size range between several hundred and 1000 Å. in diameter, in the nut shell charcoals as ordinarily prepared, in CWSC charcoal, in low density CWSN charcoals, and in highly activated (steamed) Saran charcoals. The importance of these large pores is not fully established, but they may affect the rates of adsorption of gases by the charcoal."

D. Measurements of area and pore size

Young (155) early calculated the diameter and length of the cylindrical capillary that would be required to be equivalent to the area and pore volumes of typical charcoals. For CWSN 19 using a value of 1227 sq. m. per gram for the area, he concluded that a total length of 2.05×10^{13} cm. of pores 20.8 Å. in diameter would be needed. To illustrate the enormous length of capillary thus involved, he pointed out that the length of capillary in a 1-g. sample would be equivalent to 40,000 times the circumference of the earth. If one assumes that these cylindrical capillaries are arranged as a honeycomb in a particle of charcoal, it turns out that the minimum wall thickness between the cylinders would be only about 4 Å. It is a little difficult to reconcile such a picture with the x-ray observations of platelets 10 Å. thick and 20–60 Å. wide as making up most of the charcoal. Even though cylindrical capillaries have, for convenience, been used in calculating pore diameters from water-desorption isotherms, the x-ray results, if they can be relied upon, certainly would dictate the use of caution in formulating any such picture of the charcoal structure.

Young also calculated that if all of the capillary space consists of rectangular parallelepiped capillaries with parallel walls, the distance between the walls would on an average have to be 10.4 Å. for CWSN 19, in order to account for the observed area and pore volume. Such a picture would be entirely consistent with the x-ray data. As a matter of fact, it was found that on one particular sample of CWSN charcoal, the apparent area dropped from 2040 sq. m. per gram to 1670 sq. m. per gram as the sample was heat treated up to 1100°C. During this heat treating the L_a dimension of the discs or platelets increased from 20 to 63 Å. in size. It is entirely reasonable on a platelet structure to explain such particle growth with comparatively little change in surface area. It would be much more difficult to explain if the charcoal consisted of a honeycomb structure of cylindrical capillaries.

E. Chemical behavior of charcoal

It is well known that standard charcoals can all be converted by proper chemical treatment into compounds that appear to have a central nucleus of carbon atoms arranged much as though they were in a plane of graphite. Thus mellitic acid has been reported (97) to be formed in good yield by controlled oxidation with nitric acid. This certainly indicated that much of the carbon is arranged in two-dimensional graphite-like sheets or platelets and again is consistent with the x-ray picture of the structure of charcoals.

F, Expansion of charcoals during adsorption

At least five different observers (14, 15, 16, 121, 121a, 121b, 140) have noted that when charcoal picks up water vapor in the higher relative pressure ranges it expands.[10] It should be noted, as pointed out by Kummer (99), that it is much easier to imagine the expansion of charcoals if they are made up of platelets capable of being pried apart[11] to some extent by entering water molecules in much the same way that various molecules can pry apart the planes of montmorillonite (79) and certain other clays (40). If the pore structure consists of a honeycomb of cylinders, the possibility of expansion seems much more limited.

---

[10] See footnote 6.

G. True density of carbon in charcoal

The true density of carbon in graphite is about 2.25 g./cc. as determined both from x-ray work and from actual density measurement. If the *c* dimension in charcoal is as large as 7.5 Å., as indicated by the x-ray work, and the *a* dimension is substantially the same as for graphite, it would seem to follow that the apparent density of the carbon in charcoal cannot be as high as 2.25, since the *c* distance for graphite is only 6.7 Å. As a matter of fact, on the basis of the x-ray measurements the density should be somewhere between 2.0 and 2.1. Carbon densities determined by helium have been reported over the entire range from 1.77 to 2.36 for various charcoals; a large number of the apparent densities are in the range 1.95–2.15. Accordingly, it may be said that the density values of the carbon in charcoals are also consistent with the x-ray data. It should be noted in this connection that an interplanar distance of 3.75 Å. that one would deduce from the *c* dimension is probably too small to permit the entrance of helium atoms between planes during density measurements. Hence, the density determinations on helium would really yield values for the density of the platelets.

H. General conclusion as to structure

As stated in the introduction to this section, it is not possible to speak with certainty as regards the structure of charcoal. When all of the evidence listed above is taken as a whole, however, it seems to favor capillaries of rectangular cross section for the most part, rather than cylindrical capillaries. Immediately, one is confronted with the question as to what happens to the very nice calculations of pore diameter made by Juhola if the pores are really box-like structures rather than cylinders. The answer is that the distance between parallel walls that one calculates from the Kelvin equation is just one-half as great as the diameter calculated from cylindrical capillaries. Accordingly, capillaries which with a $\cos\theta$ of 1.0 appeared to be about 36 Å. in diameter if present as cylinders would calculate to be 18 Å. between parallel platelets. However, the calculation of the distance between parallel planes from the relation of the increment of surface area A covered up by each increment of volume V is given by the equation:

$$d = \frac{2\Delta V}{\Delta A} \tag{29}$$

Hence if $\cos\theta$ were taken as 0.53, the measurement of the slope of the surface area *vs.* volume of water curve would lead to a value of about 9 Å. for the distance d. This, in the writer's opinion, is too small a size to permit the occurrence of what we might call capillary condensation. On the other hand, if one assumes that the charcoal is made up of platelets and accepts the distance *d* as 18–20 Å., the surface area per gram of charcoal is about 800 sq. m. per gram compared to values ranging from 1300 to 1700 for CWSN 19 that would be obtained by different methods of estimating the area. Possibly the answer to the dilemma is to be found by assuming that the capillaries are for the most part rectangular in cross section and for CWSN 19 about 18–20 Å. between platelets, and that even smaller crevices leading off the 20 Å. openings become covered with adsorbed water only when the larger 20 Å. openings are full. In desorption, this would mean that the water was desorbed by capillary condensation from the hemicylindrical surface at the edge of the rectangular capillary opening. This explanation is, furthermore, not inconsistent with the value of *d* obtained from equation 29, because such a calculation is necessarily an average for the main capillaries and any smaller side capillaries that fill and empty at the same time as the main 20 Å. capillaries fill and empty. It does, however, entail assuming that $\cos \theta = 1$, an assumption that does not seem very reasonable at relative pressures at which water vapor is only slightly adsorbed.

---

[11] The water molecules probably do not penetrate in between the graphite-like layers of each platelet but do enter the space between the platelets.

Possibly the capillaries are neither cylinders nor rectangular parallelepipeds, but some irregular collection of openings of odd shapes that will not permit of any simple presentation. The final answer still seems obscured. As stated above, however, if the choice were between cylindrical capillaries and rectangular capillaries the bulk of the evidence would, in the writer's opinion, favor the latter.

XII. REFERENCES

(1) Aharoni, J., and Simon, F.: Z. physik. Chem. **4B**, 175 (1929).
(2) Alekseevskiĭ, E. V., and Likharev, N. A.: J. Gen. Chem. (U.S.S.R.) **12**, 306 (1942); Chem. Abstracts **37**, 2913 (1943).
(3) Allmand, A. J.: J. Phys. Chem. **33**, 1682 (1924).
(4) Allmand, A. J.: Proc. Roy. Soc. (London) **A120**, 193 (1930).
(5) Allmand, A. J.: Trans. Faraday Soc. **28**, 225 (1932).
(6) Allmand, A. J., and Burrage, L. J.: J. Soc. Chem. Ind. **47**, 372 (1928).
(7) Allmand, A. J., and Chaplin, R.: Proc. Roy. Soc. (London) **A129**, 235 (1930).
(8) Allmand, A. J., and King, R. B.: Proc. Roy. Soc. (London) **A130**, 210 (1930).
(9) Allmand, A. J., and Lizius, J. L.: Proc. Roy. Soc. (London) **A134**, 554 (1932).
(10) Allmand, A. J., and Manning, J. E.: J. Soc. Chem. Ind. **47**, 369 (1928).
(11) Anderson, J. S.: Z. physik Chem. **88**, 191 (1914).
(12) Anderson, R. B.: J. Am. Chem. Soc. **68**, 686 (1946).
(13) Anderson, R. B., and Emmett, P. H.: To be published.
(14) Bangham, D. H.: Proc. Roy. Soc. (London) **A147**, 175 (1934).
(15) Bangham, D. H., and Razouk, R. I.: Trans. Faraday Soc. **33**, 1459 (1937).
(16) Bangham, D. H., and Razouk, R. I.: Trans. Faraday Soc. **33**, 1463 (1937).
(17) Barrer, R. M.: J. Chem. Soc. **1936**, 1261.
(18) Barrer, R. M.: J. Soc. Chem. Ind. **64**, 130 (1945).
(19) Barrer, R. M., and Ibbitson, D. A.: Trans. Faraday Soc. **40**, 195, 206 (1944).
(20) Beebe, R. A., Beckwith, J. B., and Honig, J. M.: J. Am. Chem. Soc. **67**, 1554 (1945).
(21) Beeck, O.: Rev. Modern Phys. **17**, 61 (1945).
(22) Bente, P. F., and Walton, J. H.: J. Phys. Chem. **47**, 329 (1943).
(23) Berl, E.: Trans. Faraday Soc. **34**, 1042 (1938).

(24) Blacet, F. E.: NDRC Informal Report, August 10, 1943.

(25) Blench, E. A., and Garner, W. E.: J. Chem. Soc. **1924,** 1288.

(26) Broad, D. N., and Foster, A. G.: J. Chem. Soc. **1945,** 372.

(27) Brunauer, S.: *The Adsorption of Gases and Vapors*, p. 444. Princeton University Press, Princeton, New Jersey (1943).

(28) Brunauer, S., Deming, L. S., Deming, W. E., and Teller, E.: J. Am. Chem. Soc. **62,** 1723 (1940).

(29) Brunauer, S., Emmett, P. H., and Teller, E.: J. Am. Chem. Soc. **60,** 309 (1938).

(30) Brunner, R: Z. Elektrochem. **38,** 58 (1932).

(31) Cassie, A. B. D.: Trans. Faraday Soc. **41,** 450 (1945).

(32) Colburn, A. P.: NDRC Informal Report, April 15, 1942.

(33) Colburn, A. P.: NDRC Informal Report, June 17, 1942.

(34) Colburn, A. P.: OSRD Formal Report, September 1, 1942.

(35) Chaplin, R.: Proc. Roy. Soc. (London) **A121,** 344 (1928).

(36) Cohan, L. H.: J. Am. Chem. Soc. **60,** 433 (1938).

(37) Cohan, L. H.: J. Am. Chem. Soc. **66,** 48 (1944).

(38) Coolidge, A. S.: J. Am. Chem. Soc. **48,** 1795 (1926).

(39) Coolidge, A. S.: J. Am. Chem. Soc. **49,** 708 (1927).

(40) Cornet, I.: J. Chem. Phys. **11,** 5, 217 (1943).

(41) Culbertson, J. L., and Winter, L. L.: J. Am. Chem. Soc. **63,** 95 (1941).

(42) Davis, R. T., De Witt, T. W., and Emmett, P. H.: J. Phys. Collòid Chem. **51,** 1232 (1947).

(43) Deitz, V. R., and Gleysteen, L. F.: J. Research Natl. Bur. Standards **29,** 191 (1942).

(44) Denbigh, K. G.: Trans. Faraday Soc. **36,** 936 (1940).

(45) Dewey, C. S., and Lefforge, P. K.: Ind. Eng. Chem. **24,** 1045 (1932).

(46) Dole, M., and Klotz, I. M.: Ind. Eng. Chem. **38,** 1289 (1946).

(46a) See, however, summary of mass transfer theory by Thiele: Ind. Eng. Chem. **38,** 646 (1946).

(47) Drake, L. C., and Ritter, H. L.: Ind. Eng. Chem., Anal. Ed. **17,** 787 (1945).

(48) Emmett, P. H.: *Advances in Colloid Science*, edited by E. O. Kraemer, pp. 1–36. Interscience Publishers, Inc., New York (1942).

(49) Emmett, P. H.: American Society for Testing Materials, Symposium on New Methods for Particle Size Determination in Subsieve Range, 1941, p. 95.

(50) Emmett, P. H.: Ind. Eng. Chem. **37,** 639 (1945).

(51) Emmett, P. H.: NDRC Informal Report, December 22, 1941.

(52) Emmett, P. H.: NDRC Informal Report, January 13, 1943.

(53) Emmett, P. H.: J. Am. Chem. Soc. **68,** 1784 (1946).

(54) Emmett, P. H., and Anderson, R. B.: J. Am. Chem. Soc. **67,** 1492 (1945).

(55) Emmett, P. H., and Brunauer, S.: J. Am. Chem. Soc. **59,** 1553 (1937).

(56) Emmett, P. H., and De Witt, T. W.: Ind. Eng. Chem. Anal. Ed. **13,** 28 (1941).

(57) Emmett, P. H., and De Witt, T. W.: J. Am. Chem. Soc. **65,** 1253 (1943).

(58) Emmett, P. H., and Holmes, J.: NDRC Informal Report, November 12, 1943.

(59) Emmett, P. H., Holmes, J., Anderson, R. B., Kummer, J. T., Mace, C. V., and Jenkins, J. E.: OSRD Formal Report, May 30, 1945.

(59a) Holmes, J., and Emmett, P. H.: J. Phys. Colloid Chem. **51,** 1263 (1947).

(60) Emmett, P. H., Holmes, J., and Kummer, J. T.: NDRC Informal Report, August 15, 1942.

(61) Emmett, P. H., Holmes, J., and Kummer, J. T.: NDRC Informal Report, December 15, 1942.

(62) Emmett, P. H., Holmes, J., Kummer, J. T., and Mace, C. V.: NDRC Informal Report, September 11, 1943.

(63) Emmett, P. H., Holmes, J., Kummer, J. T., Mace, C. V., and Anderson, R. B.: OSRD Formal Report, April 20, 1945.

(64) Emmett, P. H., Holmes, J., Pohl, H. A., and Kummer, J. T.: NDRC Informal Report, May 27, 1943.
(65) Emmett, P. H., Pohl, H. A., Holmes, J., and Kummer, J. T.: Division 10 NDRC Formal Report, September, 1943.
(66) Emmett, P. H., Pohl, H. A., and Kummer, J. T.: NDRC Informal Report, May 15, 1942.
(67) Emmett, P. H., Pohl, H. A., and Kummer, J. T.: NDRC Informal Report, July 8, 1943.
(68) Fineman, M. N., Guest, R. M., and McIntosh, R.: Can. J. Research **24B,** 109 (1946).
(69) Foster, A. G.: J. Chem. Soc. **1945,** 769, 773.
(70) Foster, A. G.: Trans. Faraday Soc. **28,** 645 (1932).
(71) Garner, W. E., and Kingman, F. E. T.: Trans. Faraday Soc. **25,** 24 (1929).
(72) Gleysteen, L. F., and Deitz, V. R.: J. Research Natl. Bur. Standards **35,** 285 (1945).
(73) Goldmann, F., and Polanyi, M.: Z. physik. Chem. **132,** 321 (1928).
(74) Gregg, S. J.: Proceedings of the Conference on Ultra-fine Structure of Coals and Cokes, British Coal Utilisation Research Association, **1944,** 110–17.
(75) Harkins, W. D., and Jura, G.: J. Am. Chem. Soc. **66,** 919, 1362 (1944).
(76) Harkins, W. D., and Jura, G.: J. Am. Chem. Soc. **66,** 1366 (1944).
(77) Harkins, W. D., and Jura, G.: Phys. Rev. **67,** 61 (1945).
(78) Harkins, W. D., Jura, G., and Loeser, E. H.: J. Am. Chem. Soc. **68,** 554 (1946).
(79) Hendricks, S. B., Nelson, R. A., and Alexander, L. T.: J. Am. Chem. Soc. **62,** 1457 (1940).
(80) Hill, T. L.: J. Am. Chem. Soc. **68,** 535 (1946).
(81) Hill, T. L.: J. Chem. Phys. **14,** 46 (1946).
(82) Hofmann, U., and Sinkel, F.: Z. anorg. allgem. Chem. **245,** 85 (1940).
(83) Holmes, J., and Emmett, P. H.: J. Phys. Colloid Chem. **51,** 1276 (1947).
(84) Johnstone, H. F., and Clark, G. L.: OSRD Formal Report, December 9, 1942.
(85) Johnstone, H. F., and Clark, G. L.: NDRC Informal Report, April 9, 1942.
(86) Johnstone, H. F., and Clark, G. L.: NDRC Informal Report, August 31, 1942.
(87) Johnstone, H. F., Clark, G. L., and Le Tourneau, R. L.: OSRD Formal Report, August 3, 1943.
(88) Joyner, L. G., Weinberger, E. B., and Montgomery, C. W.: J. Am. Chem. Soc. **67,** 2182 (1945).
(89) Juhola, A. J.: Dissertation, University of Rochester, Rochester, New York, 1946.
(90) Juhola, A. J.: Division 10 NDRC Formal Report, June, 1945.
(91) Juhola, A. J., and Blacet, F. E.: NDRC Informal Report, January 24, 1945.
(92) Juhola, A. J., and Skei, T.: NDRC Informal Report, June 28, 1944.
(93) Juza, R., and Langheim, R.: Z. Elektrochem. **45,** 689 (1939).
(94) Keyes, F. G., and Marshall, M. J.: J. Am. Chem. Soc. **49,** 156 (1927).
(95) King, A.: J. Chem. Soc. **1937,** 1489.
(96) King, A., and Lawson, C. G.: Trans. Faraday Soc. **30,** 1094 (1934).
(97) Kobe, K. A.: J. Chem. Education **8,** 236 (1931).
(98) Kraemer, E. O.: In *Treatise on Physical Chemistry*, edited by H. S. Taylor, p. 1661, D. Van Nostrand Co., Inc., New York (1931).
(99) Kummer, J. T.: Thesis, Johns Hopkins University, Baltimore, Maryland, 1946.
(100) Lamb, A. B.: Ind. Eng. Chem. **11,** 429 (1919).
(101) Lamb, A. B., and Woodhouse, J. C.: J. Am. Chem. Soc. **58,** 2637 (1936).
(102) Lambert, J. D.: Trans. Faraday Soc. **32,** 452 (1936).
(103) Lawson, C. G.: Trans. Faraday Soc. **32,** 473 (1936).
(104) Lemieux, R. U., and Morrison, I. A.: Can. J. Research, to be published.
(105) Lepin: Physik. Z. Sowjetunion **4,** 282 (1933).

(106) Ley, P. H. van der, and Wibaut, J. P.: Rec. trav. chim. **51**, 1143 (1932).
(107) Lizius, J. L., and Allmand, A. J.: Proc. Roy. Soc. (London) **A169**, 25 (1938).
(108) Loisy, R.: Bull. soc. chim. **6**, 46 (1939); **5**, 1509 (1938).
(109) Loisy, R.: Bull. soc. chim. **7**, 698 (1940).
(110) Loisy, R.: Bull. soc. chim. **7**, 702 (1940).
(111) London, F.: Z. physik. Chem. **11B**, 222 (1930).
(112) Lowry, H. H.: J. Am. Chem. Soc. **46**, 824 (1924).
(113) Lowry, H. H., and Hulett, G. A.: J. Am. Chem. Soc. **42**, 1393 (1920).
(114) Lowry, H. H., and Hulett, G. A.: J. Am. Chem. Soc. **42**, 1408 (1920).
(115) Maggs, F. A. P.: Proceedings of the Conference on Ultra-fine Structure of Coals and Cokes, British Coal Utilisation Research Association, **1944**, 95–109.
(116) Reference 115, pp. 147–50.
(117) Maggs, F. A. P.: Bull. Brit. Coal Utilisation Research Assoc. **9**, 253 (1945).
(118) Marshall, M. J., and Findlay, R. A.: Can. J. Research **18B**, 35 (1940).
(119) Marshall, M. J., and MacInnes, A. S.: Can. J. Research **15B**, 75 (1937).
(120) McBain, J. W.: *The Sorption of Gases and Vapours by Solids.* Routledge & Sons, London (1932).
(121) McBain, J. W., Porter, J. L., and Sessions, R. F.: J. Am. Chem. Soc. **55**, 2294 (1933).
(121a) Haines, R. S., and McIntosh, R.: J. Chem. Phys. **15**, 28 (1947).
(121b) Wiig, E. O., and Juhola, A. J.: To be published.
(122) McKie, D.: J. Chem. Soc. **1928**, 2870.
(123) Morrison, J. A., and McIntosh, R.: Can. J. Research **24B**, 137 (1946).
(124) Müller, S., and Cobb, J. W.: J. Chem. Soc. **1940**, 177.
(125) National Carbon Co.: NDRC Informal Report, June 10, 1942.
(126) National Carbon Co.: NDRC Informal Report, August 10, 1944.
(127) National Carbon Co.: NDRC Monthly Summary Report, September 15, 1944.
(128) Ockrent, C.: J. Chem. Soc. **1934**, 291.
(129) Pickett, G.: J. Am. Chem. Soc. **67**, 1958 (1945).
(130) Ramsay, W., and Shields, J.: Phil. Trans. **184A**, 647 (1893); J. Chem. Soc. **63**, 1089 (1893).
(131) Reyerson, L. H., and Wishart, A. W.: J. Phys. Chem. **42**, 679 (1938).
(132) Rhead, T. F. E., and Wheeler, R. V.: J. Chem. Soc. **103**, 461 (1913).
(133) Ritter, H. L.: Discussion at the Gibson Island A.A.A.S. Conference, 1946.
(134) Ritter, H. L., and Drake, L. C.: Ind. Eng. Chem., Anal. Ed. **17**, 782 (1945).
(135) Ruff, V. T.: Kolloid-Z. **38**, 270 (1935).
(136) Shilov, N., Shatunovska, H., and Chmutov, K.: Z. physik. Chem. **149A**, 211 (1930).
(137) Shilov, N., Shatunovska, H., and Chmutov, K.: Z. physik. Chem. **150A**, 31 (1930).
(138) Schmidt, O.: Z. physik. Chem. **133**, 780 (1928).
(139) Shull, C. G.: Discussion at the Gibson Island A.A.A.S. Conference, 1946; also, see Shull, C. G.: J. Am. Chem. Soc. **70**, 1405 (1948) and Shull, C. G., Elkin, P. B., and Roess, L. C.: J. Am. Chem. Soc. **70**, 1410 (1948).
(140) Schwab, G. M., and Karkalos, B.: Z. Elektrochem. **47**, 345 (1941).
(141) Shah, M. S.: J. Chem. Soc. **1929**, 2661, 2676.
(142) Stenhouse, J: Ann. Chem. Pharm. **101**, 243 (1897).
(143) Stock, A. von, Lux, H., and Rayner, J. W. R.: Z. anorg. Chem. **195**, 158 (1931).
(144) Stratton, G. W., and Winkler, D. E.: Ind. Eng. Chem. **34**, 603 (1942).
(145) Volman, D. H., Doyle, G. J., and Blacet, F. E.: OSRD Formal Report, April 23, 1945.
(146) Vreedenberg, H. A., and Van Nouhuys, H. L.: Rec. trav. chim. **65**, 235 (1946).
(147) Washburn, E. W.: Proc. Natl. Acad. Sci. U. S. **7**, 115 (1921).
(148) Wicke, E.: Z. Elektrochem. **44**, 587 (1938).

(149) Wiig, E. O.: Private communication.
(150) Wiig, E. O., and Flagg, J. F.: NDRC Informal Report, June, 1943.
(151) Wiig, E. O., Madison, J. J., and Juhola, A. J.: Monthly Progress Report to CWS. February, 1946; to be published.
(152) Wooten, L. A., and Brown, C.: J. Am. Chem. Soc. **65**, 113 (1943).
(153) Young, T. F.: OSRD Formal Report, September 7, 1944.
(154) Young, T. F.: OSRD Formal Report, May 22, 1945.
(155) Young, T. F.: NDRC Report, June 18, 1941.
(156) Zabor, J. W., and Juhola, A. J.: NDRC Informal Report, February 11, 1944.
(157) Volman, D. H., and Klotz, I. M.: J. Chem. Phys. **14**, 642 (1946).

THE CHEMICAL REACTIONS OF PENTAERYTHRITOL AND ITS DERIVATIVES

S. F. MARRIAN

Imperial Chemical Industries Limited, Nobel Division, Nobel House, Stevenston, Ayrshire, Scotland

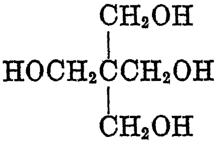
Received November 21, 1947

CONTENTS

I. Introduction 149
II. Configuration 150
III. Halides 152
  A. Chlorides 152
  B. Bromides 153
  C. Iodides 154
  D. Mixed halides 156
IV. Esters 157
V. Ethers 159
VI. Oxacyclobutane and 2,6-dioxaspiro[3.3]heptane derivatives 160
VII. Acetals and ketals 164
VIII. Amines 167
IX. 2,6-Diazospiro[3.3]heptane and trimethylenimine derivatives 181
X. Sulfur-containing derivatives 182
  A. Tetrakis(mercaptomethyl)methane 182
  B. Thio ethers, sulfoxides, and sulfones 186
  C. 2,6-Dithiaspiro[3.3]heptane 187
  D. 2,6,7-Trithiaspiro[3.4]octane 189
  E. 2,3,7,8-Tetrathiaspiro[4.4]nonane 192
XI. 2,6-Diselenaspiro[3.3]heptane 193
XII. Compounds with arsenic and boron 193
XIII. Spiranes 195
XIV. Dipentaerythritol 197
XV. Higher polypentaerythritols 198
XVI. References 198

I. INTRODUCTION

Pentaerythritol, or tetramethylolmethane, is the tetrahydric alcohol



$$HOCH_2\overset{\overset{\displaystyle CH_2OH}{|}}{\underset{\underset{\displaystyle CH_2OH}{|}}{C}}CH_2OH$$

and when pure is a colorless crystalline material melting without decomposition at 263°C. It can be sublimed under reduced pressure (58). It is soluble in about 18 parts of water at 15°C., and can be recrystallized readily from hot water. It is also soluble to some extent in alcohol, acetone, dioxane, pyridine, and liquid ammonia.

Pentaerythritol was first prepared by Tollens and Wigand (146) in 1891 by the action of formaldehyde on acetaldehyde in the presence of lime. Many modifications of the reaction have been reported in the patent literature, but essentially the same reaction is used today for the commercial production of pentaerythritol. A process in which caustic soda replaces the lime is also in operation commercially. The reaction takes place in one operation, but it can be represented as taking place in two stages:

$$CH_3CHO + 3CH_2O \xrightarrow{Ca(OH)_2} C(CH_2OH)_3CHO$$

$$C(CH_2OH)_3CHO + CH_2O + \tfrac{1}{2}Ca(OH)_2 \rightarrow C(CH_2OH)_4 + HCOOCa\tfrac{1}{2}$$

Pentaerythritol has been manufactured in large quantities during the last few years for conversion to its explosive tetranitrate. It has also a large potential market as a component in resinous compositions.

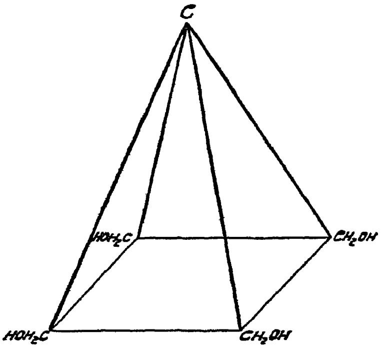


FIG. 1

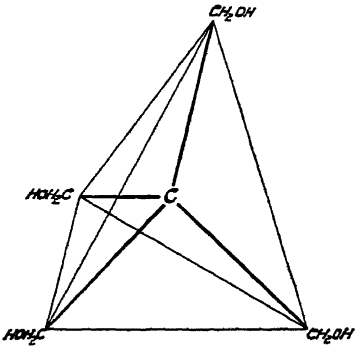


FIG. 2

This review is concerned only with the chemical reactions undergone by pentaerythritol and its derivatives which give non-polymeric products. The known derivatives of pentaerythritol have been tabulated and their melting and boiling points are listed. The indexes of *Chemical Abstracts* have been searched up to 1946 and references uncovered during general reading in 1947 are included.

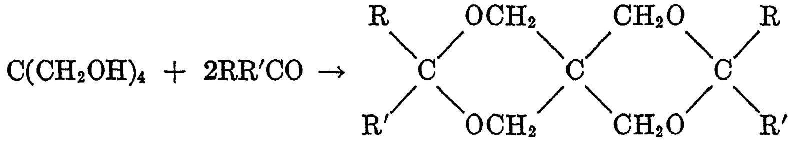
II. CONFIGURATION

Early work on x-ray examinations of the crystal structure of pentaerythritol by Mark and Weissenberg (104) and Huggins and Hendricks (85) seemed to point to a pyramidal grouping of the four CH_2OH groups around the central carbon atom (figure 1) in place of the generally accepted tetrahedral distribution (figure 2), and work on the external symmetry of the crystals by Westenbrink and van Melle (151) and by Giebe and Scheibe (65) was supposed to confirm this.

However Mark and Weissenberg, and Huggins and Hendricks, accepted the class C_{4v} originally given by Martin (105), being unaware that Haga and Jaeger (81) had shown by means of a Laue photograph that the planes of symmetry supposed to intersect in the tetrad axis were non-existent. The C_{4v} class was therefore unacceptable and various papers on this point followed.

Armed with the evidence of Liebisch (95) that the pyroelectric test gave positive results for the crystals, and of Giebe and Scheibe (65) that a positive result was obtained for the piezoelectric test, Weissenberg (150) and Reis (128) developed a new stereochemistry for the carbon atom, based on its possible nontetrahedral form. Nitta (117) and Hendricks (83) repeated the x-ray investigation and showed that the results were consistent with either a pyramidal (C_4) or a sphenoidal (S_4) symmetry of the pentaerythritol molecule. A number of publications on the crystallographic aspects of the problem were presented at about this time and the literature up to 1928 was summarized by K. Lonsdale (98). Further studies by, for example, Knaggs (90), Möller and Reis (108), Mark and Susich (103), and Llewellyn, Cox, and Goodwin (97) of pentaerythritol and its derivatives finally agreed upon a tetrahedral configuration about the central carbon atom. Raman spectrum analysis (112) and dipole moment measurements were also found to favor the tetrahedral configuration (139).

An attempt was made by Böeseken and Felix (31, 32, 33) to decide between the tetrahedral and pyramidal configurations for pentaerythritol chemically, by forming spirocyclic compounds by condensation with aldehydes or ketones and attempting to resolve them.



If the configuration is tetrahedral, the acetal or ketal must be dissymmetric and capable of resolution, but if it is pyramidal, *cis–trans* isomerism would be encountered. Read (127) had previously prepared compounds of this type and had made unsuccessful attempts to resolve them.

Böeseken and Felix prepared the spirocyclic ketal from ethyl pyruvate, and after hydrolysis of the ester grouping were able to resolve the resulting acid in the normal manner with strychnine. In another experiment the dibenzylidene derivative was obtained in optically active forms by spontaneous resolution of the racemate, but this could not be repeated.

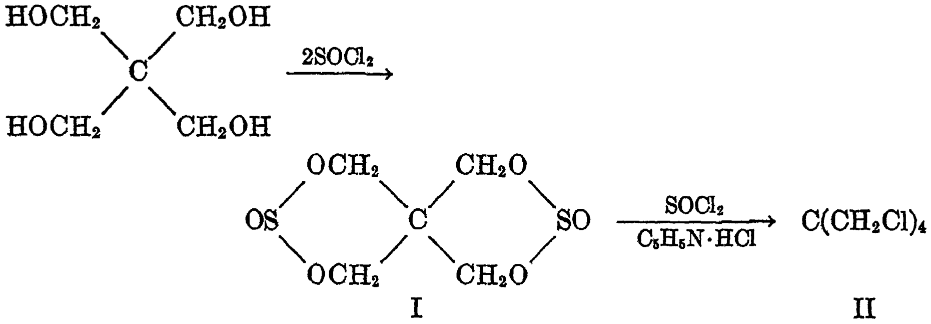
The resolution, as was pointed out by Senezov (137), does not by itself establish the tetrahedral structure of pentaerythritol, since on examination the *trans* form of the pyramidal molecule of the condensation product is seen to be dissymmetric. It has been suggested also, by Kenner (89), that chemical methods are not suitable for testing the validity of Weissenberg's principle, owing to the possibility of transformation to a tetrahedral configuration during reaction. Böeseken and Felix maintained that the enantiomorphs of the pyramidal type would be so labile as to render their isolation impossible. The accomplished resolution of the sole reaction product, together with the failure to detect any trace of *cis–trans* isomers, may therefore be taken as evidence in favor of the tetrahedral configuration.

Orthner and Freyss (119) have put forward suggestions on the spatial arrangement of the groups in the pentaerythritol molecule, based on the fact that whereas pentaerythritol gives an increase of specific conductivity in boric acid solution, disubstituted pentaerythritol derivatives, such as the dimethyl ether and dibenzoate, give no increase.

III. HALIDES

A. Chlorides

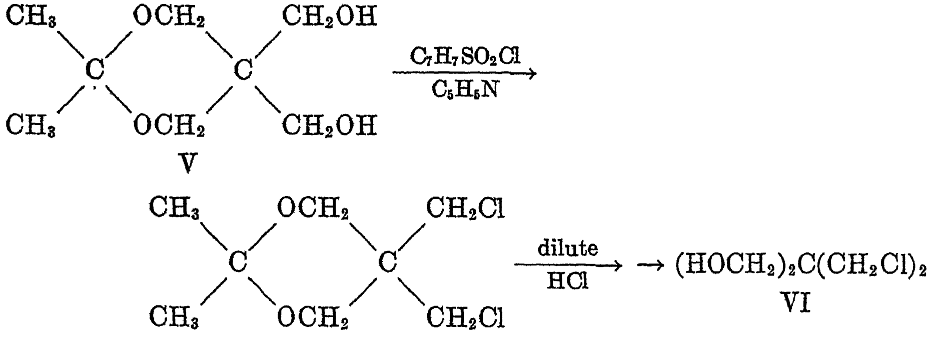
Fecht (56), in 1907, first reported that the action of concentrated hydrochloric acid on pentaerythritol at 120–180°C. gave a mixture of mono-, di-, and tri-chloro derivatives. He converted the trichloride to the tetrachloride by reaction with phosphorus trichloride at 150°C. The tetrachloride (II) has been prepared by Govaert, Hansens, and Beyaert (77) by the reaction of pentaerythritol with thionyl chloride to give the disulfite (I), followed by further reaction of this with thionyl chloride in the presence of a pyridine hydrochloride catalyst.



Mooradian and Cloke (109) have used substantially the same method for the preparation of the tetrachloride, and of mixtures of the chlorides in which either the dichloride or trichloride can be made to predominate. Their reaction is carried out in pyridine solution without intermediate isolation of the disulfite. The same authors have found that pentaerythrityl trichloride (III) is readily oxidized by nitric acid to give the corresponding trichloropivalic acid (IV).

$$\underset{\text{III}}{(CH_2Cl)_3CCH_2OH} \xrightarrow{HNO_3} \underset{\text{IV}}{(CH_2Cl)_3CCOOH}$$

Rapoport (125) has prepared pentaerythrityl dichloride (VI) uncontaminated



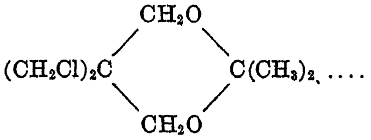
with other chloro derivatives by the action of *p*-toluenesulfonyl chloride on the monoisopropylidene derivative of pentaerythritol [2,2-dimethyl-5,5-bis(hydroxymethyl)-1,3-dioxane (V)] in the presence of pyridine, followed by opening of the dioxane ring with dilute hydrochloric acid.

The preparation of pentaerythrityl dichloride from pentaerythritol and sulfur monochloride has also been reported by Bougault (35), but his product was impure.

The pentaerythrityl chlorides and their simple derivatives are listed in table 1.

TABLE 1

Pentaerythrityl chlorides

COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$C(CH_2Cl)_4$	97	110/12 mm.; 110/12 mm.	(56, 77, 109)
$(CH_2Cl)_3CCH_2OH$	65.5 (80)	127.5–129/12 mm. (136/12 mm.)	(109) (56)
$(CH_2Cl)_2C(CH_2OH)_2$	83 (95; 65)	158.5–160/12 mm.	(56, 109) (35)
	48–49		(125)
$(CH_2Cl)_2C(CH_2ONO_2)_2$			(152)
$CH_2ClC(CH_2OH)_3$	141	190/12 mm. 183–188/16 mm.	(56) (109)
$CH_2ClC(CH_2ONO_2)_3$			(152)

B. Bromides

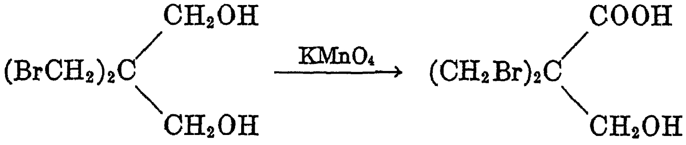
The pentaerythrityl bromides are probably the most important halides of pentaerythritol, as they are employed most frequently as starting products for the preparation of the other pentaerythritol derivatives.

Beyaert and Hansens (27) have reported a convenient method for the preparation of pentaerythrityl mono- and di-bromides, involving the reaction of pentaerythritol and hydrogen bromide in glacial acetic acid followed by saponification of the bromoacetates formed. With varying proportions of hydrogen bromide a 65 per cent yield of the monobromide together with 16 per cent of the dibromide, and an 80 per cent yield of the dibromide together with 18.5 per cent of the tribromide, were obtained. The monobromide has also been isolated by fractional distillation at 1 mm. of the mother liquors from the preparation of the dibromide (68). Barbiere and Matti (21) have prepared a mixture of the mono- and di-bromides by reaction of pentaerythritol with aqueous hydrobromic acid at 120°C. Zelinski (157) recorded the preparation of the dibromide by heating pentaerythritol and aqueous hydrobromic acid together at 125°C.; however, Bincer and Hess (28) found that by this method there is also formed a considerable proportion of the tribromide.

Hansens and Beyaert (82) have found that the tribromide is best prepared by the method of Perkin and Simonsen (121), which involves the treatment of pentaerythritol with hydrogen bromide in glacial acetic acid at 165°C. Perkin and Simonsen state that this reaction gives a mixture of the tetrabromide and the tribromide monoacetate, but state no yields. Hansens and Beyaert record a 96 per cent yield for the tribromide. Bincer and Hess (28) have prepared the tribromide from pentaerythritol and hydrobromic acid at 140°C., and Rave and Tollens (126) obtained a mixture of the tri- and tetra-bromides by the reaction of pentaerythritol with phosphorus tribromide at 100–150°C.

Schurink has reported that pentaerythrityl tetrabromide can be prepared conveniently in 86 per cent yield, without the use of a pressure vessel, by the reaction of pentaerythritol with phosphorus tribromide at an elevated temperature (15, 135). The preparation of this compound has also been reported by numerous other workers (60, 78, 82, 121, 126). Perkin and Simonsen (121) recorded the surprising unreactivity of the tetrabromide and attributed this in some degree to its insolubility. Dostrovsky, Hughes, and Ingold (48) point out that as pentaerythrityl tetrabromide is a substituted neopentyl bromide, its bimolecular substitutions are of necessity sterically hindered.

Glattfeld and Schneider (67) have oxidized pentaerythrityl dibromide with permanganate, and obtained the monobasic acid 1,1-bis(bromomethyl)-2-hydroxypropionic acid (VII).



$$(BrCH_2)_2C(CH_2OH)(CH_2OH) \xrightarrow{KMnO_4} (CH_2Br)_2C(COOH)(CH_2OH)$$

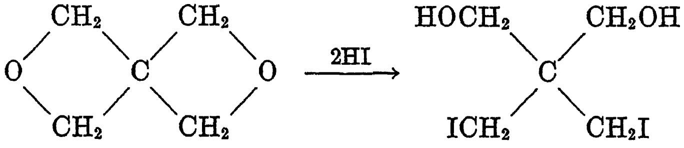
VII

The pentaerythrityl bromides and their derivatives are listed in table 2.

C. Iodides

Pentaerythrityl monoiodide has only been prepared as a by-product; it was isolated by Govaert and Beyaert (68) from the mother liquors from the preparation of the diiodide, by fractional distillation at 1 mm.

The diiodide has been prepared by Tollens and Wigand (146) by the reaction of pentaerythritol with hydriodic acid and red phosphorus at 170–180°C.; also by Bincer and Hess (28), who obtained improved yields (45 per cent) by a similar method. By treatment of pentaerythritol with the same reagent at 190°C., Tollens and Wigand (146) and Rave and Tollens (126) obtained the triiodide, together with a little tetraiodide. The tetraiodide is, however, best prepared by the action of sodium iodide on the tetrabromide in methyl ethyl ketone solution, as reported by Backer and Schurink (15, 135). The diiodide has also been obtained by Backer and Keuning (14) by the reaction of hydriodic acid with 2,6-dioxaspiro[3.3]heptane (VIII).



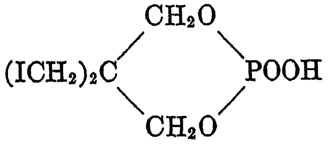
VIII

TABLE 2

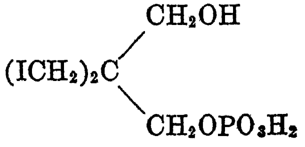
Pentaerythrityl bromides and derivatives

COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$C(CH_2Br)_4$	162		(15)
$(CH_2Br)_3CCH_2OH$	66–67 70–71		(27) (28)
$(CH_2Br)_3CCH_2OCOCH_3$	44–45		(121)
$(CH_2Br)_2C(CH_2OH)_2$	109–110 112		(28) (157)
$(CH_2Br)_2C(CH_2OCOCH_3)_2$	42	125/13 mm.	(14) (157)
$(CH_2Br)_2C(CH_2OCOC_6H_5)_2$	92		(27)
$(CH_2Br)_2C(CH_2OCOC_6H_4NO_2\text{-}p)_2$	211		(27)
$CH_2BrC(CH_2OH)_3$	76		(68)
$CH_2BrC(CH_2OCOCH_3)_3$	50	159/0.04 mm.	(27)

Eidebenz and Depner (50) have recorded that from the reaction of pentaerythrityl diiodide with phosphorus oxychloride they isolated calcium salts derived from the following acids:



and



Bincer and Hess (28) have converted the diiodide, by reaction with silver acetate and subsequent acetylation, into pentaerythritol tetraacetate, and by catalytic hydrogenation in the presence of pyridine and magnesia over palladinized barium sulfate, into 2,2-dimethyltrimethylene glycol.

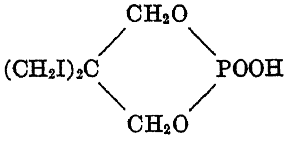
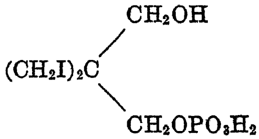
The melting points of the pentaerythrityl iodides are listed in table 3.

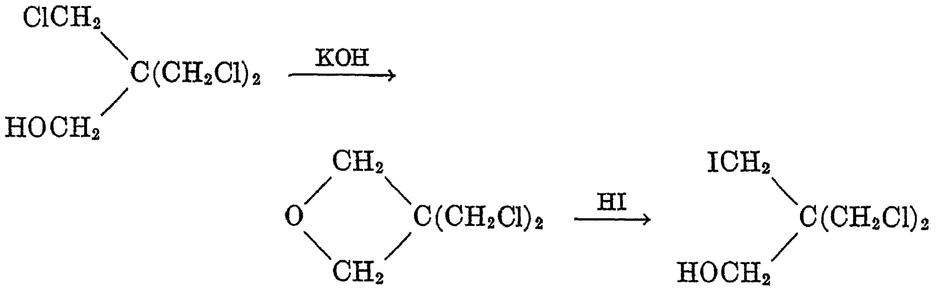
D. Mixed halides

Govaert and Beyaert (72) have prepared mixed trihalogen derivatives indirectly by splitting off hydrogen halide from pentaerythrityl trichloride or tribromide with potassium hydroxide to obtain the corresponding oxacyclobutane derivative (IX), and then opening the ring with another halogen hydride to produce the mixed trihalide. The ring closure was reported to give 70–80 per cent yields and the ring opening quantitative yields.

TABLE 3

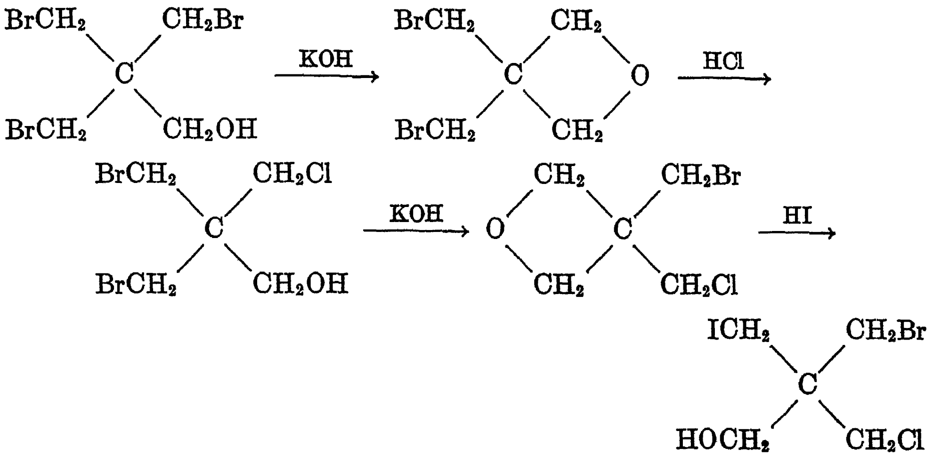
Pentaerythrityl iodides

COMPOUND	MELTING POINT	REFERENCES
	°C.	
$C(CH_2I)_4$	233	(15, 135)
$(CH_2I)_3CCH_2OH$	62	(146)
$(CH_2I)_2C(CH_2OH)_2$	129.5–130.5	(28)
$CH_2IC(CH_2OH)_3$	106	(68)
	Isolated as Ca salt	(50)
	Isolated as Ca salt	(50)



IX

3,3-Bis(iodomethyl)oxacyclobutane was prepared by the action of sodium iodide on an acetone solution of the corresponding dibromide. (Chloromethyl)(bromomethyl)(iodomethyl)ethanol (X) was prepared by the following series of reactions:



X

The melting points of the mixed trihalogen derivatives are recorded in table 4.

TABLE 4

Mixed trihalides of pentaerythritol

COMPOUND	MELTING POINT	REFERENCES
	°C.	
$HOCH_2C(CH_2Cl)_2(CH_2Br)$	55	(72)
$HOCH_2C(CH_2Cl)_2(CH_2I)$	45	(72)
$HOCH_2C(CH_2Br)_2(CH_2Cl)$	55	(72)
$HOCH_2C(CH_2Br)_2(CH_2I)$	54	(72)
$HOCH_2C(CH_2I)_2(CH_2Cl)$	58	(72)
$HOCH_2C(CH_2I)_2(CH_2Br)$	55	(72)
$HOCH_2C(CH_2Cl)(CH_2Br)(CH_2I)$	51	(72)

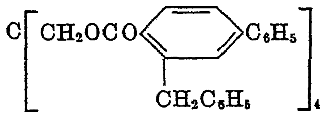
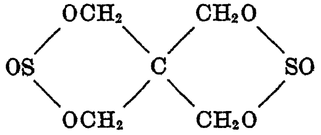
IV. ESTERS

There are many references in the literature to the resinous esters of pentaerythritol which are prepared from polybasic acids, resin acids, or unsaturated acids. These polymeric materials are omitted from this review.

The tetraesters from pentaerythritol and monobasic acids can be prepared readily from pentaerythritol by the usual methods of reaction with acids, acid chlorides, or acid anhydrides. Barth and Burrell (22) have reported suitable conditions for the preparation of the mono-, di-, and tri-esters from pentaerythritol and the corresponding pentaerythrityl tetraester in the presence of an alkaline catalyst, such as potassium carbonate, at elevated temperatures. Savary (133) has found that esterification of fatty acids with an excess of pentaerythritol in boiling phenol gives mainly monoesters, which can be purified from the other esters by fractional crystallization. Diesters of pentaerythritol have been prepared indirectly by Orthner and Freyss (119) by esterification of the monoisopropylidene derivative, followed by hydrolysis of the ketal grouping.

TABLE 5

Simple esters of pentaerythritol

COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$C(CH_2OCOH)_4$	57		(130)
$(CH_2OH)_3CCH_2OCOCH_3$			(22)
$(CH_2OH)_2C(CH_2OCOCH_3)_2$		207–215/2 mm. 159/0.3 mm.	(22) (119)
$CH_2OHC(CH_2OCOCH_3)_3$		176–182/2 mm.	(22)
$C(CH_2OCOCH_3)_4$	84–86	 155–160/2 mm.	(121, 146) (158)
$C(CH_2OCOCH_2CH_3)_4$	25–30	170–175/2 mm.	(84, 158)
$C[CH_2OCO(CH_2)_2CH_3]_4$		185–190/2 mm.	(158)
$(CH_2OH)_3CCH_2OCO(CH_2)_8CH_3$		Light oil	(159)
$(CH_2OH)_3CCH_2OCO(CH_2)_{10}CH_3$	75		(39, 102, 133)
$C[CH_2OCO(CH_2)_{10}CH_3]_4$	48.8–49		(102)
$(CH_2OH)_3CCH_2OCO(CH_2)_{12}CH_3$	89		(102, 133)
$C[CH_2OCO(CH_2)_{12}CH_3]_4$	62		(102)
$(CH_2OH)_3CCH_2OCO(CH_2)_{14}CH_3$	96		(102, 133)
$C[CH_2OCO(CH_2)_{14}CH_3]_4$	70–70.5		(1, 2)
$(CH_2OH)_3CCH_2OCO(CH_2)_{16}CH_3$	46–47		(25, 133)
$(CH_2OH)_2C[CH_2OCO(CH_2)_{16}CH_3]_2$	51–52		(25)
$C[CH_2OCO(CH_2)_{16}CH_3]_4$	76.2 60–61		(102) (25)
$C[CH_2OCO(CH_2)_7CH{=}CH(CH_2)_7CH_3]_4$			(29)
$C[CH_2OCOCH{=}CHCH_3]_4$			(49)
$(CH_2OH)_2C(CH_2OCOC_6H_5)_2$	75		(119)
$C(CH_2OCOC_6H_5)_4$	99–101 94		(126) (119)
$(CH_2OH)_3CCH_2OCOC_6H_4NO$-*o*	105		(144)
			(57)
$C(CH_2ONO_2)_4$	138–140		(149)
	153–154		(35, 76, 118)
$C(CH_2OSO_3H)_4$			(92)
$C(CH_2OSO_3)_4Ba_2$			(92)
$C(CH_2OSO_3CH_3)_4$	110.5		(92)
$C[CH_2OCOOCH_2C(CH_3){=}CH_2]_4$			(111)

The acid tetrasulfate has been prepared from pentaerythritol by Kraft (92) by the action of chlorosulfonic acid, and is easily isolated through its soluble barium salt.

The simple non-polymeric esters which have been prepared from pentaerythritol are listed in table 5.

Van Romburgh (130) has observed that pentaerythrityl tetraformate is split up quantitatively on heating to give carbon monoxide and pentaerythritol. Pentaerythrityl tetraacetate has been found by Baltzly and Buck (20) to be completely hydrolyzed when 0.01 mole of ester in 35–50 cc. of methanol is allowed to stand in contact with 5 cc. of concentrated hydrochloric acid for 24 hr.

With the exception of pentaerythrityl tetranitrate, which is employed for its explosive properties, few of the simple esters have found much commercial application. A few mixed esters have been claimed in the patent literature for use as modifying agents in resins and as explosives, and other esters have been suggested for use in insecticides and as lubricating oil additives (34, 88). Muskat and Strain (111) have prepared pentaerythrityl tetrakis(methallyl carbonate) and have found that it polymerizes with benzoyl peroxide at 140°C. The mixed esters can be prepared by further esterification of mono-, di-, and tri-esters; a method has also been claimed for the preparation of mixed esters containing the acetyl radical from pentaerythritol in the presence of an organic acid and ketene (123).

TABLE 6

Mixed esters of pentaerythritol

COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	*°C.*	
Diformate dinitrate			(152)
Diacetate dinitrate			(152)
Diacetate dipropionate		173–188/2 mm.	(22)
Diacetate dibutyrate		160–165/2 mm.	(22)
Triacetate monopropionate		162–164/2 mm.	(22)
Triacetate monostearate			(130, 159)
Tripropionate monomyristate			(129, 158)
Diglycolic ester, tetranitrate		Liquid	(152)
Mono-*m*-nitrobenzoate trinitrate	50–55		(152)
Mono-*o*-nitrosobenzoate tribenzoate	86–88		(144)

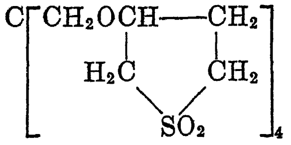
The mixed esters of pentaerythritol which have been reported are listed in table 6.

V. ETHERS

The tetraethers from pentaerythritol can be formed readily, and the most convenient method is generally the reaction of pentaerythrityl tetrabromide with the sodium derivative of the alcohol or phenol (5). Ether formation has also been accomplished by the reaction of an alkyl halide with pentaerythritol in presence of alkali (42, 116) and by the reaction of alkyl halide with the sodium derivative of pentaerythritol in liquid ammonia (66). Gustavson and Popper have recorded the preparation of the tetraethyl ether of pentaerythritol by the action of alcoholic potash on pentaerythrityl tetrabromide (80). Pentaerythritol has also been reported to react with acrylonitrile (40) and with butadiene sulfone (17) to give tetrakis(2-cyanoethoxymethyl)methane (XI) and tetrakis-(1,1-dioxy-3-thiophanyloxymethyl)methane (XII), respectively.

$C(CH_2OCH_2CH_2CN)_4$

XI



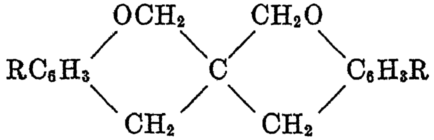
XII

Bruson (41) has found that with crotononitrile, or with allyl cyanide under alkaline conditions (which cause the conversion of the latter to the former), pentaerythritol reacts to give a mixture of bis-, tris-, and tetrakis-(2-cyanoisopropyl) ethers.

The di-*tert*-butyl ether of pentaerythritol has been prepared by the action of *tert*-butyl chloride on pentaerythritol in pyridine solution (5), and the mono-, di-, and tri-methyl ethers of pentaerythritol have been prepared by Orthner and Freyss (119) from monoisopropylidene pentaerythritol.

When pentaerythritol reacts with allyl bromide or methallyl bromide in presence of caustic soda, three ether groupings are introduced. This product can then be converted to the tetraether by reaction with sodium and more of the bromide (115, 116).

Backer and Dijken (5) have examined the action of aluminum chloride on aromatic ethers of pentaerythritol. The tetraphenyl ether gives an isomer for which the structure $C(CH_2C_6H_4OH)_4$ is suggested, although it does not react with acetyl chloride. This isomer is also formed when pentaerythrityl tetrabromide reacts with sodium in boiling phenol. The tetra-*p*-chlorophenyl ether and the tetra-*p*-tolyl ether also react in the presence of aluminum chloride to give products to which the structures XIII and XIV are assigned.



XIII: R = Cl

XIV: R = CH_3

The *p*-tolyl ether also produces a small quantity of an isomer, $C_{33}H_{36}O_4$. Bowman and Barth (36) have reported the action of alkene oxides on pentaerythritol and polypentaerythritols to give ether-alcohol derivatives.

The ethers of pentaerythritol which have been prepared are listed in table 7.

VI. OXACYCLOBUTANE AND 2,6-DIOXASPIRO[3.3]HEPTANE DERIVATIVES

Pentaerythritol, as a polyhydric alcohol, can form intramolecular ether linkages to give a 3,3-disubstituted oxacyclobutane (XV) or 2,6-dioxaspiro[3.3]heptane (XVI).

TABLE 7

Ethers from pentaerythritol

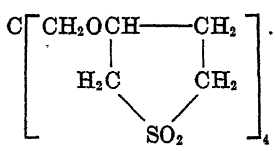
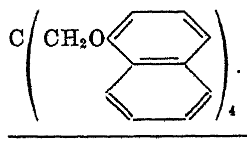
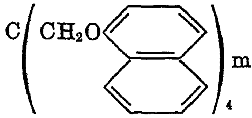
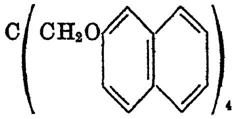
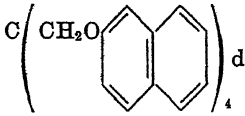
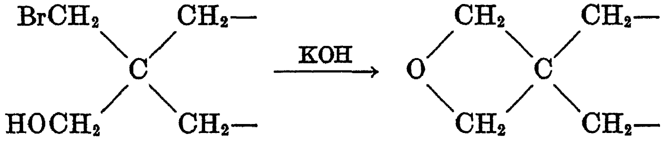
COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$(CH_2OH)_3CCH_2OCH_3$	72		(119)
Monoisopropylidene derivative		129–130/12 mm.	
p-Nitrobenzoate of monoisopropylidene derivative	90		
$(CH_2OH)_2C(CH_2OCH_3)_2$	32	139/12 mm.	(119)
$(CH_2OH)_2C(CH_2OCH_3)_2$ dibenzoate	70		
$CH_2OHC(CH_2OCH_3)_3$		103–104/12 mm.	(119)
$CH_2OHC(CH_2OCH_3)_3$ *p*-nitrobenzoate	53–54		
$C(CH_2OCH_3)_4$	30–30.5	196–198	(5)
$(CH_2OH)_3CCH_2OC_2H_5$			(42)
$(CH_2OH)_2C(CH_2OC_2H_5)_2$		116/5 mm.	(42, 66)
$CH_2OHC(CH_2OC_2H_5)_3$		94/5 mm.	(42, 66)
$C(CH_2OC_2H_5)_4$		230–231; 83/5 mm.	(5, 66, 80)
$C[CH_2O(CH_2)_2CH_3]_4$		124–127/3 mm.	(5)
$CH_2OHC(CH_2OCH_2CH{=}CH_2)_3$		114–122/1 mm.	(116)
$C(CH_2OCH_2CH{=}CH_2)_4$		124–125/1 mm.	(114, 116)
$CH_2OHC[CH_2OCH_2C(CH_3){=}CH_2]_3$		135–140/0.8 mm.	(115)
$C[CH_2OCH_2C(CH_3){=}CH_2]_4$		128–129/0.3 mm.	(115)
$(CH_2OH)_2C[CH_2OC(CH_3)_3]_2$	102–104		(5)
$C(CH_2OC_{16}H_{33})_4$	57.5–59		(5)
$C(CH_2OC_6H_5)_4$	112.5–113.5		(24)
$C(CH_2OC_6H_4Cl\text{-}p)_4$	141–142		(5)
$C(CH_2OC_6H_4Br\text{-}p)_4$	153–157		(5)
$C(CH_2OC_6H_4CH_3\text{-}p)_4$	96		(5)
$C[CH_2OC_6H_4C(CH_3)_3\text{-}p]_4$	168–169		(5)
$C[CH_2OC_6H_3Br(o?)C(CH_3)_3\text{-}p]_4$	231–232		(5)
$C[CH_2OC_6H_4C(CH_3)_2(C_2H_5)\text{-}p]_4$	193–194.5		(5)
$C(CH_2OCH_2C_6H_5)_4$		246–250/3 mm.	(5)
$C[CH_2OC(C_6H_5)_3]_4$	350		(148)
	222.5–223.5		(17)
$C(CH_2OCH_2CH_2CN)_4$			(40)
$C(CH_2OCH_2CH_2COOC_4H_9)_4$		Not distillable at 1 mm.	(40)
$C(CH_2OCH_2CH_2CONH_2)_4$			(40)
	170–171.5		(5)

TABLE 7—*Concluded*

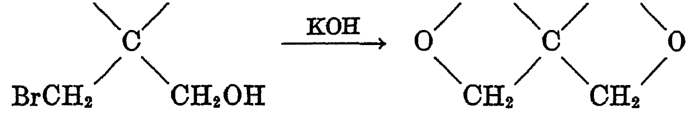
COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
 monopicrate......	200–201.5		
	119–120		(5)
 dipicrate..........	189.5–190.5		
$CH_3OCH_2C(CH_2ONO_2)_3$	79–80		(131, 152)
$(CH_3OCH_2)_2C(CH_2ONO_2)_2$............ .	53–54		(152)
$C_2H_5OCH_2C(CH_2ONO_2)_3$................			(132)

The general method for the preparation of oxacyclobutane derivatives is by the action of potassium hydroxide on a pentaerythrityl halide (26, 59, 70, 71, 72).



XV

Attempts made to prepare 2,6-dioxaspiro[3.3]heptane by the action of sodium on pentaerythrityl dibromide, potassium hydroxide on pentaerythrityl dibromide diacetate, sulfuric acid on pentaerythritol, and potassium hydroxide on pentaerythrityl dichloride were all without success. Backer and Keuning (14) obtained the required material by the action of alcoholic potash on pentaerythrityl dibromide.



XVI

2,6-Dioxaspiro[3.3]heptane is a solid which is volatile at ordinary temperatures. The ether linkages are split readily with hydriodic acid to give 2,2-bis(iodomethyl)-1,3-propanediol.

Oxacyclobutane and dioxaspiroheptane derivatives prepared from pentaerythritol are listed in table 8.

TABLE 8

Oxacyclobutane and 2,6-dioxaspiro[3.3]heptane derivatives prepared from pentaerythrito

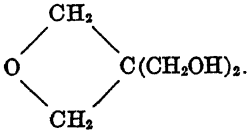
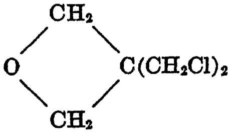
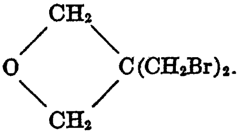
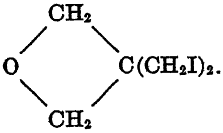
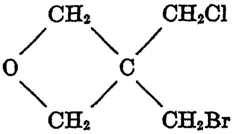
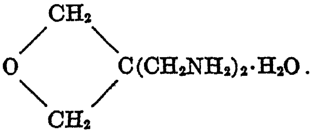
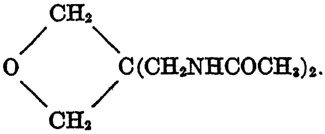
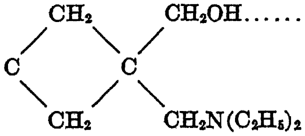
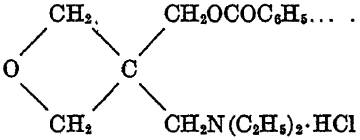
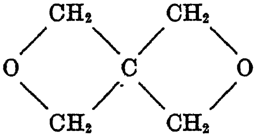
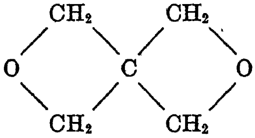
COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
	84	128/0.04 mm.	(71)
	19		(72)
	25	121/1.8 mm.	(26, 72)
	49		(72)
	16		(72)
		122/1.5 mm.	(26)
Dihydrochloride	234		(26)
Dipicrate	237 d.		(26)
Dioxalate	154 d.		(26)
	79		(26, 70)
		132/14 mm.	(59)
Hydrochloride	135.5		(59)

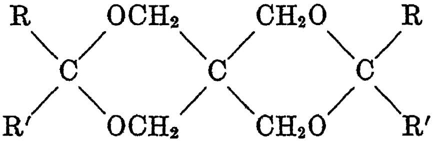
TABLE 8—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
	142		(59)
	89	172	(14)
 + 1.5HgCl$_2$	130–132		(14)

VII. ACETALS AND KETALS

Pentaerythritol readily forms acetals and ketals, and these have been the subject of a fair volume of work on account of their spirocyclic nature.

$2RR'CO + C(CH_2OH)_4 \longrightarrow$



$+ 2H_2O$

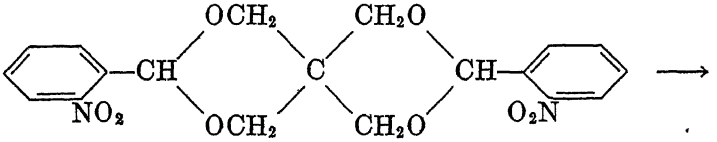
Tollens (4, 134), Read (127), and Radulescu (124) used hydrochloric and sulfuric acids as condensing agents with a variety of aldehydes. Böeseken and Felix (31) have used alcoholic hydrogen chloride for the preparation of ketals from carboxylic ketones, and Backer and Schurink (16) have employed zinc chloride. Mkhitaryan (107) found that pentaerythritol diacetals can be prepared in good yield, uncontaminated by the monoacetals, by the reaction of pentaerythritol with acetals in the presence of a small quantity of *p*-toluenesulfonic acid. Orthner (118) has used anhydrous copper sulfate as a condensing agent.

The preparation of monoacetals and monoketals from pentaerythritol has been reported by Böeseken (30, 31, 32, 33), Skrabal (140, 141), Orthner (118, 119), Tanasescu (143, 144), Fairbourne and Woodley (53), and British Celanese Ltd. (38). Their separation from the corresponding diacetals and diketals can generally be accomplished by solubility differences. Fairbourne and Woodley found that when 50 per cent sulfuric acid was used as the condensing agent for *p*-dimethylaminobenzaldehyde and pentaerythritol the proportion of monoacetal was much higher than when 10 per cent sulfuric acid was used. These authors, and also Tanasescu and Iliescu (144), have found that on attempting to prepare a mixed acetal from a monoacetal, by reaction with another aldehyde, the original alkylidene radical was eliminated with formation of the diacetal derived from the second aldehyde.

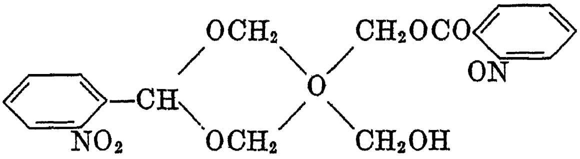
Nieuwland, Vogt, and Foohey (113) have prepared diethylidenepentaerythritol from pentaerythritol and acetylene in the presence of a boron trifluoride–alcohol–mercury catalyst.

Böeseken and Felix (31) have reported that in a preparation of the dibenzylidene acetal of pentaerythritol from benzylidene acetal and pentaerythritol, they obtained an optically active product by spontaneous resolution of the racemate. They were unable to repeat the preparation, but have resolved other acetals and ketals by the usual methods (32, 33).

Tanasescu (143, 144, 145) has investigated the action of sunlight on the di-*o*-nitrobenzylidene acetal of pentaerythritol (XVII). The material developed a yellow color, and only one of the acetal groupings was affected, the product being the mono-*o*-nitrosobenzoate of mono-*o*-nitrobenzylidenepentaerythritol (XVIII).



XVII



XVIII

The crude reaction product was separated into two isomers, both of which gave the same benzoate; on hydrolysis both gave the same *o*-nitrobenzylidenepentaerythritol. One isomer was converted to the other on careful heating and it is suggested that they are *cis* and *trans* isomers. Mono-*o*-nitrobenzylidenepentaerythritol also undergoes reaction in sunlight, being converted to pentaerythritol mono-*o*-nitrosobenzoate.

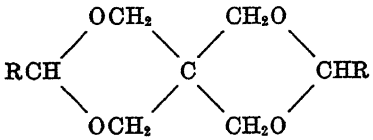
Contardi and Ciocca (44) have recorded that formaldehyde, at ordinary temperature, reacts with pentaerythritol to give an equilibrium mixture containing the hemiacetal.

A method for the estimation of pentaerythritol as its dibenzylidene derivative has been reported by Kraft (91).

It has been claimed by Scott (136) that the dimethylene ether of pentaerythritol is a suitable medium for the reaction of sodium with certain hydrocarbons (e.g., naphthalene). When the sodium derivatives formed are treated with carbon dioxide, carboxylic acids result.

TABLE 9

Acetals from pentaerythritol



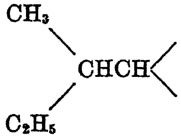
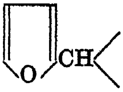
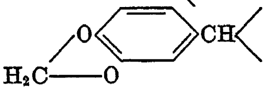
$RCH<$	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$CH_2<$	50		(127, 134, 141)
$CH_3CH<$		113/14 mm.	(113)
	40; 45		(140, 141)
$CH_3CH_2CH<$	25	250–252	(140, 141)
$CH_3(CH_2)_2CH<$	60–65		(107)
$(CH_3)_2CHCH<$	95		(140, 141)
 $\begin{matrix}CH_3 & \\ & CHCH< \\ C_2H_5 & \end{matrix}$	110–112		(107)
$CH_3(CH_2)_5CH<$	63		(127)
$CH_2ClCH<$	91.8		(107)
$CH_2(NH_2)CH<$ *dl*	62–64		(33)
l	60–70		
d	72–74		
$CCl_3CH<$	275		(31)
$CBr_3CH<$	248–249		(16)
	161		(127)
	164.5–165		(16)
$C_6H_5CH<$ *dl*	160		
d	188–189		(4, 31, 124, 127)
$o\text{-}O_2NC_6H_4CH<$	163–164		(124, 127, 143)
	166		(144, 145)
$m\text{-}O_2NC_6H_4CH<$	185		(127)
	188–189		(124)
$p\text{-}O_2NC_6H_4CH<$	229		(127)
	236–237		(124)

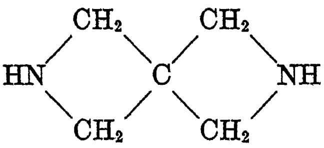
TABLE 9—*Concluded*

$RCH<$	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$o\text{-}H_2NC_6H_4CH<$ (amorphous)	164		(124)
$o\text{-}H_2NC_6H_4CH<$ hydrochloride	172		(124)
$m\text{-}H_2NC_6H_4CH<$	225		(124)
$m\text{-}(CH_3)_2NC_6H_4CH<$			(31)
$p\text{-}(CH_3)_2NC_6H_4CH<$	223		(124)
$p\text{-}(CH_3)_2NC_6H_4CH<$ monomethiodide	220 d.		(53)
$m\text{-}HO_3SC_6H_4CH<$			(31)
$m\text{-}HOOCC_6H_4CH<$			(31)
$C_6H_5CH{=}CHCH<$	195		(127)
$p\text{-}CH_3OC_6H_4CH<$	177		(127)
	188		(127)

Diacetals and diketals from pentaerythritol are listed in tables 9 and 10 and monoacetals and ketals in table 11.

VIII. AMINES

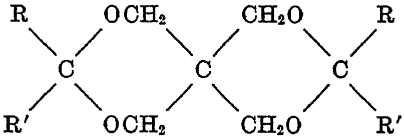
Govaert (67) first reported the preparation of the tetramine derived from pentaerythritol, $C(CH_2NH_2)_4$. Pentaerythrityl tetrabromide on reaction with liquid ammonia gave small quantities of the amine, and when heated in a sealed vessel at 180–190°C. with a saturated solution of ammonia in ethanol, a 35 per cent yield was obtained. The hydrochloride was reported to lose ammonium chloride in hot aqueous solution to give the dihydrochloride of 2,6-diazaspiro-[3.3]heptane (XIX).



XIX

TABLE 10

Ketals from pentaerythritol



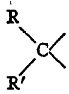
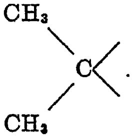
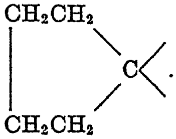
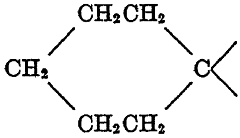
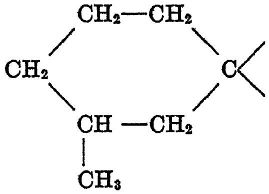
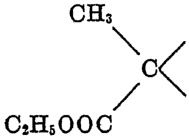
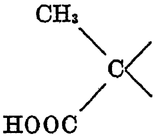
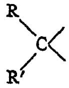
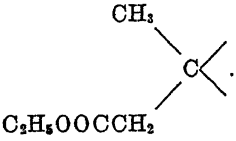
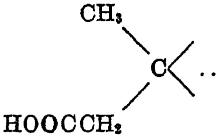
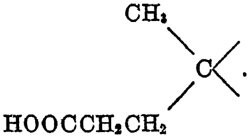
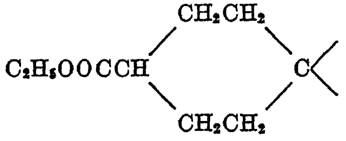
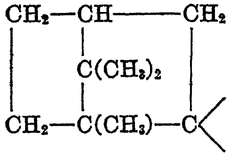
	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
	116		(30, 118, 140, 141)
	153–155		(16)
	115.5		(16)
 *d*	79–81		(30)
	46	145 130–135*	(31) (32)
	235		(31) (32)

TABLE 10—*Concluded*

	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
		145–150*	(31)
	Loses CO_2 at 100°C.		(31)
	186–188		(31)
	139.5–140.5		(122)
	156		(33)

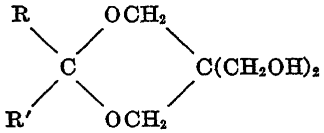
* High vacuum.

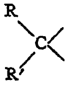
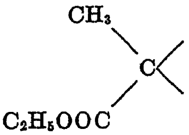
Contrary to this finding, Litherland and Mann (96) recorded that the tetrahydrochloride of the tetramine possessed great stability and was recovered unchanged from boiling in water for 36 hr., boiling in hydrochloric acid for 20 hr., and from treatment with hydrochloric acid at 160°C. for 5 hr.

Van Alphen (3) investigated the action of ammonia on pentaerythrityl tetrabromide and found that a mixture of highly condensed amines resulted, with only a little of the tetramine. Litherland and Mann (96, 100) have prepared the tetramine from pentaerythrityl tetrabromide by a two-stage process, which they claim as being convenient for the preparation of large quantities. The tetrabromide was heated with sodium *p*-toluenesulfonamide for 10 hr. at 210°C. to give tetrakis(*p*-toluenesulfonamidomethyl)methane (XX) as the chief product. On hydrolysis of this with 80 per cent sulfuric acid, the disulfate of the tetramine

TABLE 11

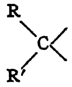
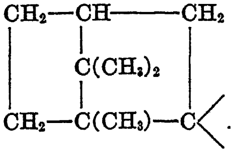
Monoacetals and ketals from pentaerythritol



 $RR'C<$	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$CH_2<$	60		(140)
$CH_2<$ diacetate		298	(38)
$CH_2<$ dipropionate		312	(38)
$CH_2<$ dibutyrate		336	(38)
$CH_2<$ dibenzoate	94–96		(38)
$CH_3CH<$	104		(140)
$CH_3CH<$ diacetate		310	(38)
$NH_2CH_2CH<$	124		(33)
$CH_3CH_2CH<$	70		(140)
$CH_3CH_2CH_2CH<$ diacetate		345	(38)
$(CH_3)_2CHCH<$	107		(140)
$(CH_3)_2C<$	135		(30, 140, 141, 118)
Diacetate	48–49		(119)
Dibenzoate	110		(119)
 $(CH_3)(C_2H_5OOC)C<$		145–165*	(31)
	95		(32)
o-$O_2NC_6H_4CH<$	145		(143)
Mono-o-nitrosobenzoate (*cis* and *trans* isomers)	85 and 135		(143)
Mono-o-nitrosobenzoate monobenzoate	83–84		(143)
Dibenzoate	109–110		(144)
Mono-o-azobenzoate	110		(144)

* High vacuum.

TABLE 11—*Concluded*

	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
p-$(CH_3)_2NC_6H_4CH<$	140 d.		(53)
p-$(CH_3)_2NC_6H_4CH<\cdot CH_3I$	175 d.		(53)
	135		(33)

was obtained and readily gave the free base, which was isolated as the tetrahydrate (63).

$$C(CH_2Br)_4 + NaNHSO_2C_6H_4CH_3 \rightarrow \underset{\text{XX}}{C(CH_2NHSO_2C_6H_4CH_3)_4}$$

$$\xrightarrow{80\%\ H_2SO_4} C(CH_2NH_2)_4 + CH_3C_6H_4SO_3H$$

Govaert and Beyaert (69) isolated the tetramine as the monohydrate.

N-Tetrasubstituted pentaerythrityltetramine derivatives can be prepared readily, and generally in good yield, by reaction of the tetrabromide with the corresponding amine (3).

$$4RNH_2 + C(CH_2Br)_4 \rightarrow C(CH_2NHR)_4\cdot 4HBr$$

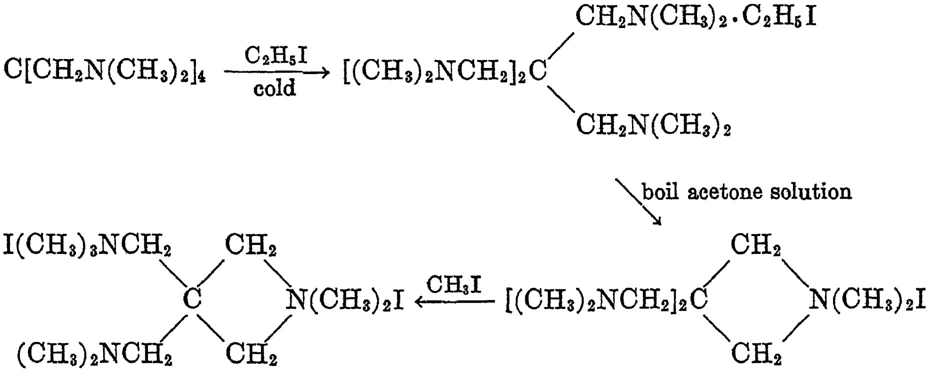
Secondary amines have also been prepared from pentaerythrityltetramine by condensation with aldehydes, followed by reduction of the products (3).

$$C(CH_2NH_2)_4 + 4RCHO \longrightarrow C(CH_2N{=}CHR)_4 \xrightarrow{H_2} C(CH_2NHCH_2R)_4$$

Litherland and Mann (96) found that methylation of pentaerythrityltetramine gave the octamethyl derivative, tetrakis(dimethylaminomethyl)methane, $C[CH_2N(CH_3)_2]_4$, and that although this gave a tetrapicrate and tetrahydrochloride, it could not be induced to combine directly with 4 molecules of methyl iodide, giving instead the biquaternary iodide $C[CH_2N(CH_3)_2]_2[CH_2N(CH_3)_3I]_2$. When this biquaternary iodide was heated above its melting point, effervescence occurred and the quadriquaternary salt, $C[CH_2N(CH_3)_3I]_4$, was isolated.

Govaert and Cazier (74) have prepared the quadriquaternary bromide $C[CH_2N(CH_3)_3Br]_4$ by the reaction of pentaerythrityl tetrabromide with trimethylamine in alcoholic solution at 230°C. for 18 hr. The same authors (75) have also reported the isolation of this compound from the product of reaction of pentaerythrityl dibromide with trimethylamine in alcoholic solution at 150°C. for 20 hr.

Gibson and Mann (64) have also studied other quaternary salts of the octamethyl base. On treatment of tetrakis(dimethylaminomethyl)methane with ethyl iodide in the cold, a monoethiodide was obtained and when this was boiled in acetone solution it was converted to 3,3-bis(dimethylaminomethyl)-*N*-methyltrimethyleneimine monomethiodide (XXI), which with an excess of methyl iodide combined with only one more molecule.



XXI

When, however, the octamethyl base was boiled with ethyl iodide, a diethiodide resulted; on heating, this was converted to the dihydriodide of the original octamethyl base with elimination of a gas, probably ethylene.

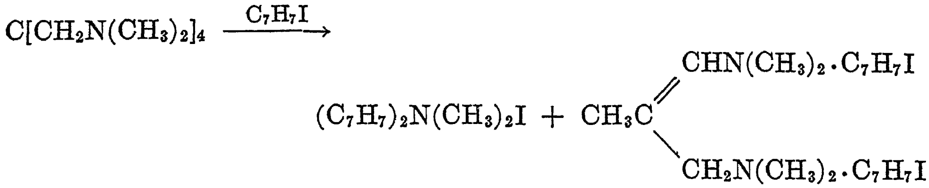
$$C[CH_2N(CH_3)_2]_4 \xrightarrow[\text{boil}]{C_2H_5I} C[CH_2N(CH_3)_2]_2[CH_2N(CH_3)_2C_2H_5I]_2 \xrightarrow{\text{heat}}$$

$$C[CH_2N(CH_3)_2]_2[CH_2N(CH_3)_2HI]_2$$

Reaction of the octamethyl base with an excess of allyl iodide in the cold produced the monoallyliodide, which, when heated, also produced 3,3-bis(dimethylaminomethyl)-*N*-methyltrimethyleneimine monomethiodide (XXI). When the monoallyliodide was treated with an excess of methyl iodide, it gave the monoallyliodide monomethiodide.

From the reaction of the octamethyl base with an excess of allyl iodide in the cold there was also produced the monoallyliodide monohydriodide, which on fusion gave the dihydriodide of the octamethyl base, a reaction similar to that of the diethiodide.

The reaction of benzyl iodide with tetrakis(dimethylaminomethyl)methane followed those with ethyl and allyl iodides, but with certain differences. When the octamethyl base and benzyl iodide were mixed without solvent, there were obtained dibenzyldimethylammonium iodide and the dibenzyl iodide of 1,3-bis(dimethylamino)-2-methylpropene (XXII).



$$C[CH_2N(CH_3)_2]_4 \xrightarrow{C_7H_7I} (C_7H_7)_2N(CH_3)_2I + CH_3C\begin{cases} =CHN(CH_3)_2\cdot C_7H_7I \\ -CH_2N(CH_3)_2\cdot C_7H_7I \end{cases}$$

XXII

When benzyl iodide was mixed with the octamethyl base in ether solution, there was obtained the monobenzyliodide of the base, the dibenzyliodide of the base, and the monobenzyliodide monohydriodide of the base. The monobenzyliodide behaved similarly to the monoethiodide and the monoallyliodide on heating, giving the trimethyleneimine derivative (XXI), and the dibenzyl iodide behaved similarly to the diethiodide on heating in giving the dihydriodide of the octamethyl base.

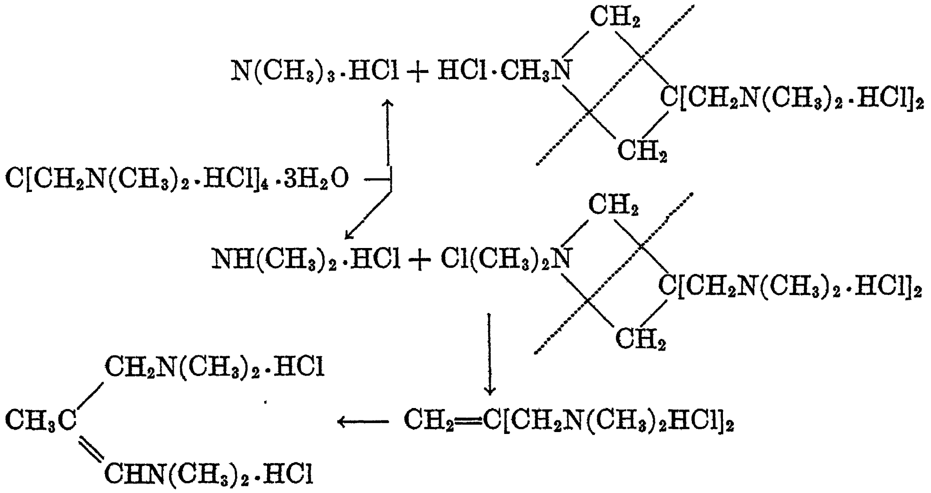
Gibson, Harley-Mason, Litherland, and Mann (63) have reported the transformations undergone by the hydrochlorides of tetrakis(methylaminomethyl)-methane, $C(CH_2NHCH_3)_4$, and tetrakis(dimethylaminomethyl)methane, $C[CH_2N(CH_3)_2]_4$, on heating. The tetrahydrochloride of the tetramethyl base when heated to just above its melting point decomposes to give the dihydrochloride of 1,3-bis(methylamino)propane (XXIII).

$$[HCl\cdot NH(CH_3)CH_2]_2C(CH_2NHCH_3\cdot HCl)_2 \longrightarrow CH_2(CH_2NHCH_3\cdot HCl)_2$$

XXIII

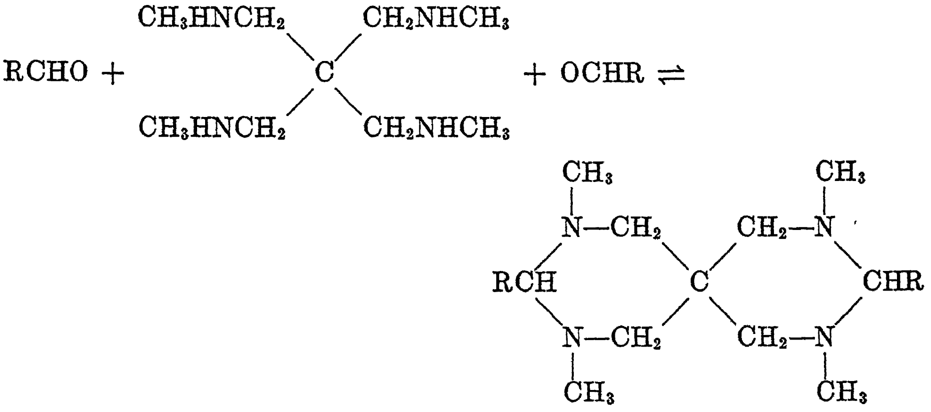
This is a reaction of the salt only, the free base being volatile without decomposition.

When the hydrated hydrochloride of the octamethyl base is heated above its melting point, formaldehyde is evolved and the residue contains the hydrochlorides of mono-, di-, and tri-methylamines, together with the hydrochloride of 1,3-bis(dimethylamino)-2-methylpropene (XXIV). The authors suggest the following mechanism:



XXIV

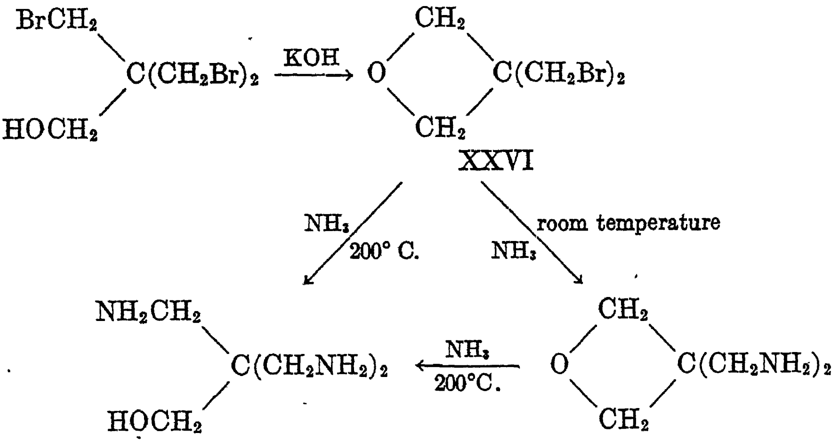
Tetrakis(methylaminomethyl)methane condenses readily with aldehydes to give derivatives of 2,4,8,10-tetramethyl-2,4,8,10-tetraazaspiro[5.5]undecane (XXV), which are readily hydrolyzed back to the amine and the aldehyde by dilute acids.



XXV

Derivatives of tetrakis(aminomethyl)methane are listed in table 12 and those of 2,4,8,10-tetramethyl-2,4,8,10-tetraazaspiro[5.5]undecane in table 13.

Beyaert and Govaert (26) have prepared the triamino derivative of pentaerythritol indirectly from pentaerythrityl tribromide. Reaction of the bromide with the theoretical amount of potassium hydroxide produced 3,3-bis(bromomethyl)oxacyclobutane (XXVI) in 79 per cent yield and from this the corresponding 3,3-bis(aminomethyl)oxacyclobutane (XXVII) was obtained by the action of liquid, alcoholic, or aqueous ammonia at room temperature. The oxacyclobutane ring was opened by aqueous ammonia at 200°C. to give the triamino compound (XXVIII). The substitution of NH_2 for Br, and the ring opening with ammonia were also carried out in one step by reaction of the bis(bromomethyl)oxacyclobutane with ammonia at 200°C.



XXVIII XXVII

TABLE 12

Derivatives of tetrakis(aminomethyl)methane

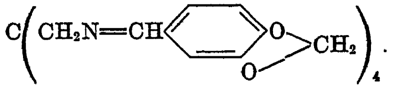
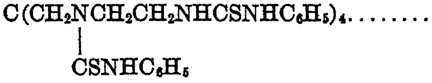
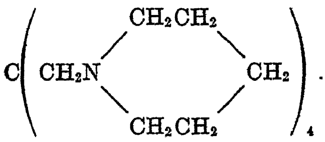
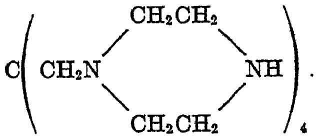
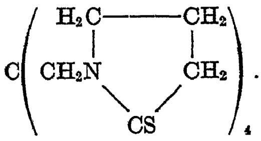
COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$C(CH_2NH_2)_4\cdot H_2O$	41–42	278–282 108/0.7 mm.	(3, 69)
$C(CH_2NH_2)_4\cdot 4H_2O$	100–100.5		(63)
$C(CH_2NH_2)_4\cdot 4HCl$	Decomposes above *ca.* 260		(96)
$C(CH_2NH_2)_4\cdot 4HBr$			(67, 69)
$C(CH_2NH_2)_4\cdot HNO_3$	220–222		(67)
$C(CH_2NH_2)_4\cdot (H_2SO_4)_2$	303		(96)
$C(CH_2NH_2)_4$ tetrapicrate	196–197		(96)
	206–208		(3)
$C(CH_2NH_2)_4\cdot 2H_2CO_3$	125 with loss of CO_2		(69)
$C(CH_2NH_2)_4\cdot 2HgCl_2$			(69)
$C(CH_2NHCOCH_3)_4$	60	72.5–73/2 mm.	(69)
$C(CH_2NHCOC_6H_5)_4$	276		(96)
$C(CH_2NHSO_2C_6H_4CH_3\text{-}p)_4$	248		(96)
$C(CH_2NHSO_2C_6H_4NH_2\text{-}p)_4$	243.5–244		(96)
$C(CH_2NHSO_2C_6H_4NHCOCH_3\text{-}p)_4$	304–306		(96)
$C(CH_2NHCONH_2)_4$	230 d.		(69)
$C(CH_2NHNH_2)_4\cdot 5HBr\cdot 3H_2O$	Decomposes at 207		(3)
$C(CH_2NHCSNHC_6H_5)_4$	Decomposes at 150		(3)
$C(CH_2N{=}CHC_6H_5)_4$	330		(3)
$C(CH_2N{=}CHC_6H_4Cl\text{-}p)_4$	272		(3)
$C(CH_2N{=}CHC_6H_4NO_2\text{-}p)_4$	178		(3)
	130		(3)
$C(CH_2NHCH_3)_4\cdot 2H_2O$		235–238	(3)
		245–248	(63)
$C(CH_2NHCH_3)_4\cdot 4HCl$	264 d.		(63)
$C(CH_2NHCH_3)_4\cdot 4HBr$	266 d.		(63)
$C(CH_2NHCH_3)_4$ tetrapicrate	190–195		(3)
$C[CH_2N(CH_3)CSNHC_6H_5]_4$	152 d.		(3)
$C[CH_2N(CH_3)SO_2C_6H_5]_4$	239		(63)
$C(CH_2NHCH_2CH_2NH_2)_4$		265–275	(3)
 $C(\underset{\displaystyle CSNHC_6H_5}{CH_2N}CH_2CH_2NHCSNHC_6H_5)_4$	130–135		(3)
$C(CH_2NHCH_2CH_2NHCH_2C_6H_5)_4$ hydrochloride	140–160 d.		(3)

TABLE 12—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	REFERENCES
	°C.	°C.	
$C(CH_2NHCH_2C_6H_5)_4$ hydrochloride	217–218		(3)
$C[CH_2N(CH_3)_2]_4$		248–249/769 mm. 157/45 mm.	(63)
$C[CH_2N(CH_3)_2]_4 \cdot 4HCl$	231		(96)
$C[CH_2N(CH_3)_2]_4 \cdot 2HI$	208–209		(64)
$C[CH_2N(CH_3)_2]_4 \cdot 2CH_3I$	149 d.		(96)
$C[CH_2N(CH_3)_2]_4 \cdot 4CH_3I$	Sublimes above 350		(96)
$C[CH_2N(CH_3)_2]_4 \cdot 4CH_3Cl$	Sublimes above 330		(74)
$C[CH_2N(CH_3)_2]_4 \cdot 4CH_3ClO_4$	Decomposes explosively at 380		(74)
$C[CH_2N(CH_3)_2]_4$ tetramethopicrate	310 d.		(74)
$C[CH_2N(CH_3)_2]_4 \cdot 2C_2H_5I$	128		(64)
$C[CH_2N(CH_3)_2]_4 \cdot C_3H_5I$	145–146		(64)
$C[CH_2N(CH_3)_2]_4 \cdot C_3H_5I \cdot HI$	157–158		(64)
$C[CH_2N(CH_3)_2]_4 \cdot C_3H_5I \cdot CH_3I$	114–115 d.		(64)
$C[CH_2N(CH_3)_2]_4 \cdot C_6H_5CH_2I$	146–147		(64)
$C[CH_2N(CH_3)_2]_4 \cdot 2C_6H_5CH_2I$	128–129 d.		(64)
$C[CH_2N(CH_3)_2]_4 \cdot C_6H_5CH_2I \cdot HI$	170		(64)
$C[CH_2N(CH_3)_2]_4 \cdot C_3H_5I \cdot C_6H_5CH_2I$	145–146 d.		(64)
	163		(3)
			(3)
	Decomposes above 320		(3)
$C[CH_2N(NO_2)C_6H_4(NO_2)_3\text{-}o,o,p]_4$	117		(3)

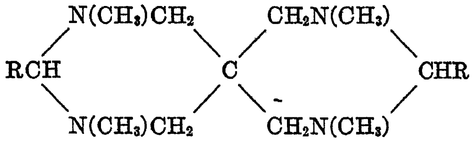
Fourneau, Matti, and Dunant (59) have prepared derivatives of the triamine by reaction of pentaerythrityl tribromide with primary and secondary amines at 130–140°C.

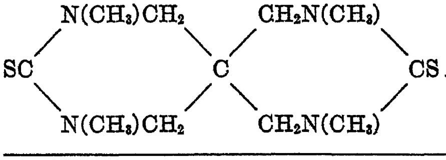
In the preparation of tetrakis(*p*-toluenesulfonamidomethyl)methane (XIX) from pentaerythrityl tetrabromide and sodium *p*-toluenesulfonamide, Litherland and Mann (96) found that there was always obtained, as a by-product, a small quantity of *N*-*p*-toluenesulfonyl-3,3-bis(*p*-toluenesulfonamidomethyl)trimethyleneimine (XXIX). Hydrolysis of the toluenesulfonyl groups and ring opening were accomplished by heating with 70 per cent sulfuric acid, giving hydroxymethyltris(aminomethyl)methane (XXVIII). This triamine gave a tetrabenzoyl derivative, but even with an excess of *o*-nitrobenzoyl chloride only the tri-*o*-nitrobenzoyl derivative could be isolated.

When the trisulfonamide derivative (XXIX) was heated with concentrated hydrochloric acid, ring opening occurred and chloromethyltris(*p*-toluenesulfonamidomethyl)methane (XXX) was formed. This reaction was reversed by caustic soda. Further hydrolysis with hydrochloric acid removed the toluenesulfonyl residues to give chloromethyltris(aminomethyl)methane (XXXI), and steam distillation of this chlorotriamine in alkaline solution converted it to 3,3-bis(aminomethyl)trimethyleneimine (XXXII). On hydrolysis of the tri-*o*-nitrobenzoyl derivative of this compound, ring fission occurred to give the monohydroxytriamine (XXVIII).

TABLE 13

2,4,8,10-Tetramethyl-2,4,8,10-tetraazaspiro[5.5]undecane derivatives

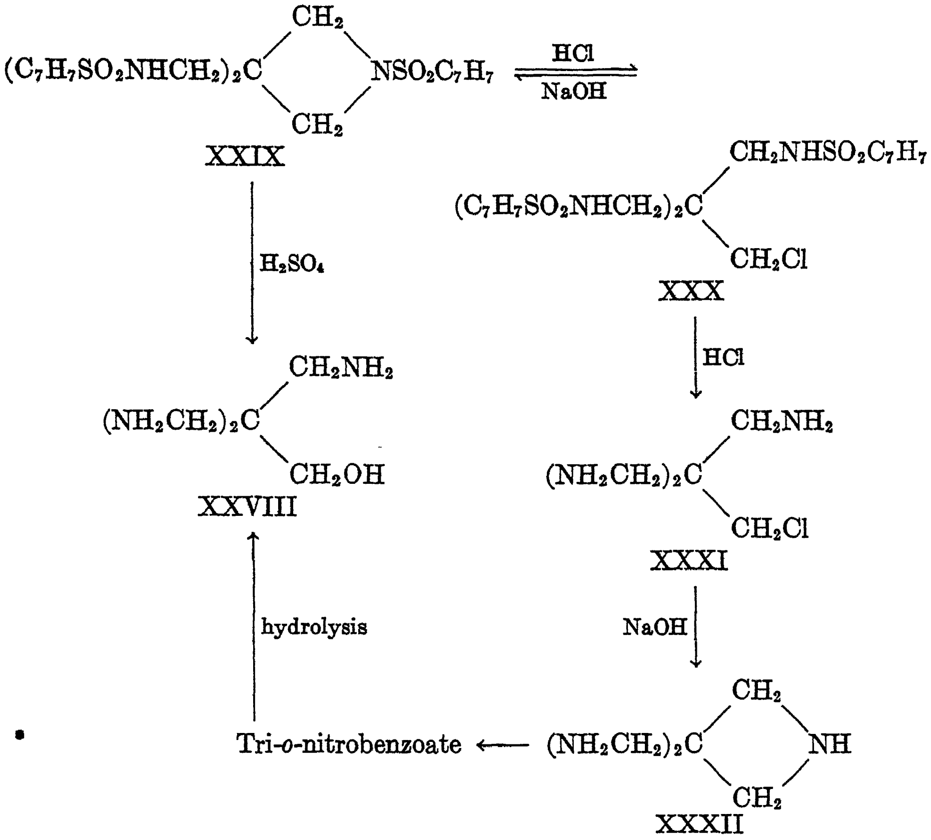


COMPOUND	MELTING POINT	REFERENCE
	°C.	
R = C_6H_5	110	(3)
= $C_6H_4NO_2$-*p*	230	(3)
= C_6H_4Cl-*p*	220	(3)
= $C_6H_4OCH_3$-*p*	164	(3)
= $C_6H_3(O_2CH_2)$ (3,4-)	153	(3)
	Decomposes at about 260	(3)

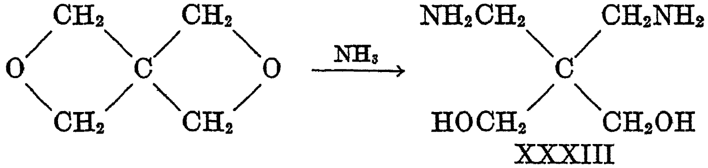
fonamidomethyl)methane (XXX) was formed. This reaction was reversed by caustic soda.

The derivatives of hydroxymethyltris(aminomethyl)methane are listed in table 14 and 3,3-disubstituted trimethyleneimine derivatives prepared from pentaerythritol are listed in table 17.

Govaert and Beyaert (70) have prepared 2,2-bis(aminomethyl)-1,3-propane-



diol (XXXIII) in 78 per cent yield by the action of aqueous ammonia on 2,6-dioxaspiro[3.3]heptane at 190°C. for 12 hr.



In an attempt to prepare this diamine from pentaerythrityl dibromide and alcoholic ammonia, they report that only 3,3-bis(acetaminomethyl)oxacyclobutane was isolated in low yield after acetylation of the reaction product. Reaction was also attempted with liquid ammonia at 100°C. and was found to occur readily, but no definite product could be separated from the reaction mixture.

Fourneau, Matti, and Dunant (59) have reported the preparation of alkyl derivatives of the diamine by reaction of pentaerythrityl dibromide with primary or secondary amines at 130–140°C.

Govaert and Cazier (75) have prepared 2,2-bis(dimethylaminomethyl)-1,3-propanediol by reacting 2,6-dioxaspiro[3.3]heptane with aqueous dimethylamine at 215°C. Derivatives of 2,2-bis(aminomethyl)-1,3-propanediol are listed in table 15.

Govaert and Beyaert (71) have also reported the preparation of the monoamine derived from pentaerythritol,—aminomethyltris(hydroxymethyl)methane. They carried out their reaction from pentaerythrityl monobromide in two stages. Reaction of the bromide with potassium hydroxide gave an 81 per cent yield of 3,3-bis(hydroxymethyl)oxacyclobutane (XXXIV) and the ring opening was accomplished with aqueous ammonia at 200°C. to give a 60 per cent yield of the monoamine (XXXV).

TABLE 14

Derivatives of hydroxymethyltris(aminomethyl)methane

COMPOUND	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
$CH_2OHC(CH_2NH_2)_3$	121	131/0.11 mm.	(26)
$CH_2OHC(CH_2NH_2)_3 \cdot 3HCl$	298 d.		(96)
$CH_2OHC(CH_2NH_2)_3 \cdot 3HNO_3$	239 d.		(26)
$CH_2OHC(CH_2NH_2)_3 \cdot 2H_2SO_4$	288		(26)
$CH_2OHC(CH_2NH_2)_3 \cdot 2H_2C_2O_4$	172		(26)
$CH_2OHC(CH_2NH_2)_3$ tripicrate	145 d.		(96)
$CH_3COOCH_2C(CH_2NHCOCH_3)_3$	58		(26)
$C_6H_5COOCH_2C(CH_2NHCOC_6H_5)_3$	231–232		(96)
$CH_2OHC(CH_2NHCOC_6H_4NO_2\text{-}o)_3$	229		(96)
$CH_2OHC(CH_2NHCH_3)_3$		142/15 mm.	(59)
$CH_2OHC(CH_2NHCH_3)_3 \cdot 3HCl$	155 (from methanol); 229 (dried)		(59)
$CH_2OHC[CH_2N(CH_3)_2]_3$		125/13 mm.	(59)
$CH_2OHC[CH_2N(CH_3)_2]_3 \cdot 3HCl$	238		(59)
$CH_2ClC(CH_2NH_2)_3$			
$CH_2ClC(CH_2NH_2)_3 \cdot 3HCl$	276		(96)
$CH_2ClC(CH_2NH_2)_3$ tripicrate	122		(96)
$CH_2ClC(CH_2NHSO_2C_7H_7)_3$	271–272		(96)
$CH_2BrC(CH_2NHSO_2C_7H_7)_3$	268		(96)

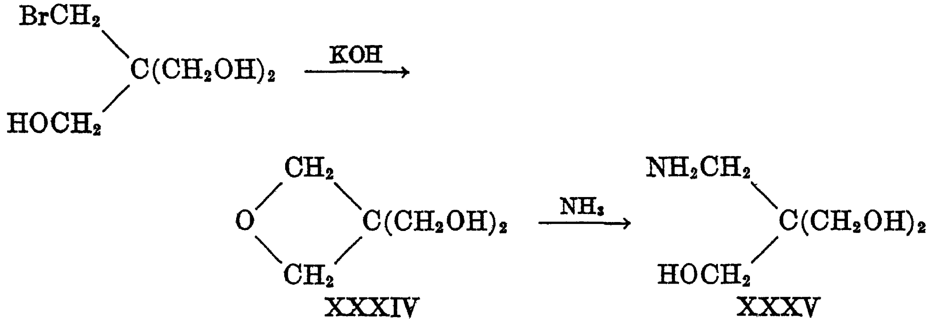
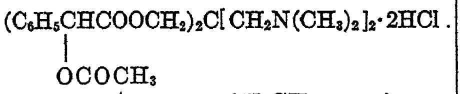
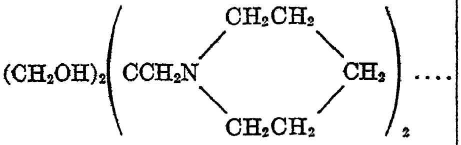


TABLE 15

Derivatives of 2,2-bis(aminomethyl)-1,3-propanediol

COMPOUND	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
$(CH_2OH)_2C(CH_2NH_2)_2 \cdot H_2O$		200/0.002 mm.	(70)
$(CH_2OH)_2C(CH_2NH_2)_2 \cdot 2H_2C_2O_4$	160 d.		(70)
$(CH_2OH)_2C(CH_2NH_2)_2 \cdot H_2CO_3$	Reverts to diamine at 164		(70)
$(CH_2OH)_2C(CH_2NH_2)_2$ dipicrate	223 d.		(70)
$(HOCH_2)(BrCH_2)C(CH_2NH_2)_2$			(73)
$(HOCH_2)(BrCH_2)C(CH_2NH_2)_2 \cdot 2HBr$			
$(BrCH_2)_2C(CH_2NH_2)_2$			(73)
$(BrCH_2)_2C(CH_2NH_2)_2 \cdot 2HBr$	286 d.		
$(CH_2OH)_2C(CH_2NHCH_3)_2$	40	185/25 mm.	(59)
$(CH_2OH)_2C(CH_2NHCH_3)_2 \cdot 2HCl$	198		(59)
$(CH_2OH)_2C(CH_2NHCH_3)_2 \cdot 2HBr$	214		(59)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2$	36	160–162/24 mm.	(59)
		137/15 mm.	(75)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2 \cdot 2HCl$	208		(59)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2 \cdot 2HBr$	207		(75)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2$ dipicrate	155		(75)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2 \cdot 2CH_3I$			(75)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2 \cdot 2CH_3Br$	185		(75)
$(CH_2OH)_2C[CH_2N(CH_3)_2]_2$ dimethopicrate	194		(75)
$(CH_3COOCH_2)_2C[CH_2N(CH_3)_2]_2$	35	151/12 mm.	(75)
$(CH_3COOCH_2)_2C[CH_2N(CH_3)_2]_2 \cdot 2CH_3I$	229		(75)
$(CH_2COOCH_2)_2C[CH_2N(CH_3)_2]_2 \cdot 2CH_3Br$	228 d.		(75)
$(CH_2COOCH_2)_2C[CH_2N(CH_3)_2]_2$ dimethopicrate	184–185		(75)
$(CH_2COOCH_2)_2C[CH_2N(CH_3)_2]_2$ dimethoperchlorate	272 d.		(75)
$(C_6H_5COOCH_2)_2C[CH_2N(CH_3)_2]_2 \cdot 2HCl$	244		(59)
 $(\underset{\textstyle OCOCH_3}{C_6H_5CH}COOCH_2)_2C[CH_2N(CH_3)_2]_2 \cdot 2HCl$	212		(59)
	84	198/4.5 mm.	(59)
$(CH_2OH)_2C[CH_2N(C_2H_5)_2]_2$		160/15 mm.	(59)

Barbiere and Matti (21) have prepared dimethylaminomethyltris(hydroxymethyl)methane directly from the monobromide and dimethylamine. Derivatives of the monoamine are listed in table 16.

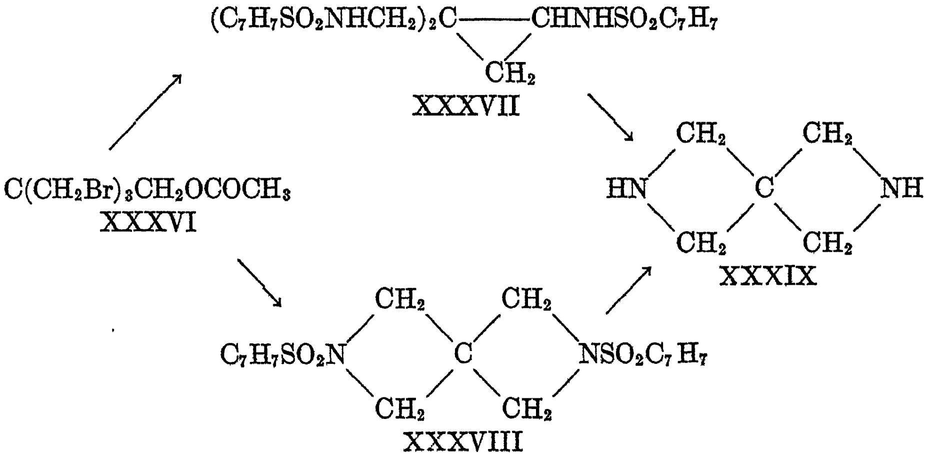
IX. 2,6-DIAZASPIRO[3.3]HEPTANE AND TRIMETHYLENIMINE DERIVATIVES

Litherland and Mann (96) have studied the action of sodium *p*-toluenesulfonamide on tris(bromomethyl)acetoxymethylmethane (XXXVI) at 180°C. and found that two compounds could be isolated: 1-*p*-toluenesulfonamido-2,2-bis(*p*-toluenesulfonamidomethyl)cyclopropane (XXXVII) and *N*,*N'*-di-*p*-toluenesulfonyl-2,6-diazaspiro[3.3]heptane (XXXVIII). When the tritoluenesulfonamido compound was hydrolyzed with hydrochloric acid, made alkaline, and steam distilled, ammonia and diazaspiroheptane (XXXIX) were produced, the latter in low yield. When the ditoluenesulfonyl compound was treated similarly, the same spirocyclic compound was obtained in higher yield.

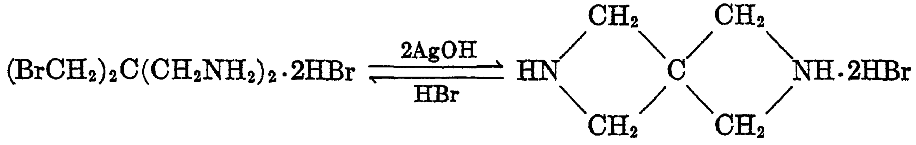
TABLE 16

Derivatives of aminomethyltris(hydroxymethyl)methane

COMPOUND	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
$(HOCH_2)_3CCH_2NH_2$	207		(71)
$[(HOCH_2)_3CCH_2NH_2]_2 \cdot H_2C_2O_4$	206		(71)
$(HOCH_2)_3CCH_2NH_2$ picrate	80		(71)
$(CH_3COOCH_2)_3CCH_2NHCOCH_3$		173/0.04 mm.	(71)
$(HOCH_2)_3CCH_2NHCOOH \cdot NH_2CH_2C(CH_2OH)_3$	149 d.		(71)
$(HOCH_2)_3CCH_2N(CH_3)_2$	51–52	178–182/4 mm.	(21)
$(HOCH_2)_3CCH_2N(CH_3)_2 \cdot HCl$	125.5		(21)



Govaert and Beyaert (73) found that the dihydrobromide of 2,6-diazaspiro-[3.3]heptane was formed when 2 molecules of hydrogen bromide were removed with silver oxide from the dihydrobromide of 2,2-bis(bromomethyl)-1,3-diaminopropane; the reaction was reversed with 66 per cent hydrobromic acid at 180°C.



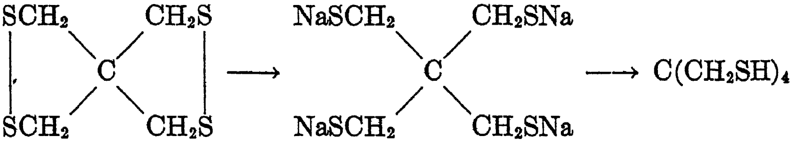
They attempted to isolate the spiro base in the free state, but found that polymerization always occurred.

Derivatives of 2,6-diazaspiro[3.3]heptane and of trimethylenimine which have been prepared from pentaerythritol are listed in table 17.

X. SULFUR-CONTAINING PENTAERYTHRITOL DERIVATIVES

A. *Tetrakis(mercaptomethyl)methane*

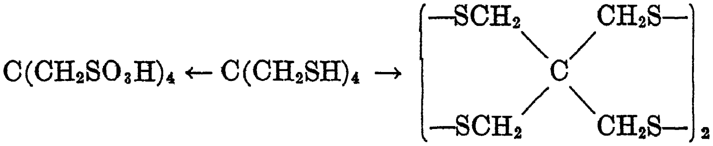
The tetrathio derivative of pentaerythritol, tetrakis(mercaptomethyl)methane (XL), has been prepared by Backer and Evenhuis (11) by the reduction of 2,3,7,8-tetrathiaspiro[4.4]nonane (XXXIX) (see page 193) with sodium in liquid ammonia, and treatment of the product with acid to decompose the sodium salt.



XXXIX XL

Tetrakis(mercaptomethyl)methane has also been prepared by Farlow and Signaigo (54) from the polymeric product obtained by the action of sodium tetrasulfide on pentaerythrityl tetrabromide, by hydrogenation in dioxane solution over a cobalt polysulfide catalyst.

Tetrakis(mercaptomethyl)methane is a solid, m.p. 73–73.5°C., which gives solid mercaptides with many heavy metals, and on oxidation with hydrogen peroxide in acetic acid gives the corresponding tetrasulfonic acid (XLI). Oxidation of the sodium derivative with iodine is reported to give a dimer (XLII).



XLI XLII

The tetramercaptan condenses readily with aldehydes and ketones in the presence of hydrochloric acid to give solid derivatives of 2,4,8,10-tetrathiaspiro-

TABLE 17

Trimethylenimine derivatives prepared from pentaerythritol, and 2,6-diazaspiro [3.3]heptane derivatives

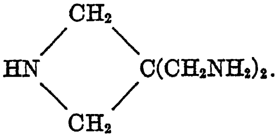
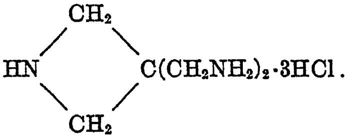
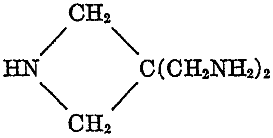
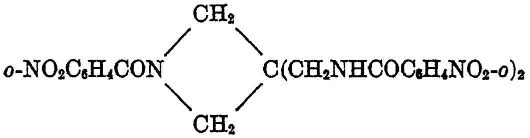
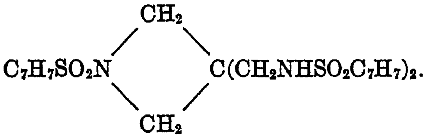
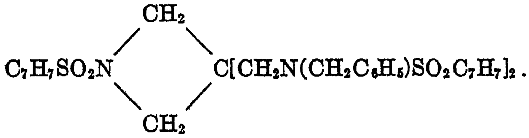
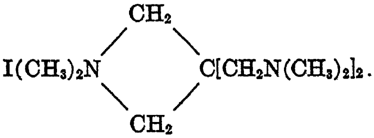
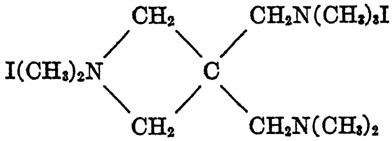
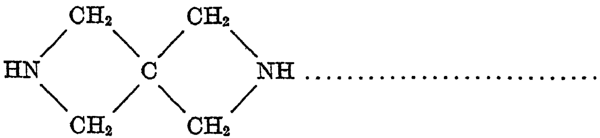
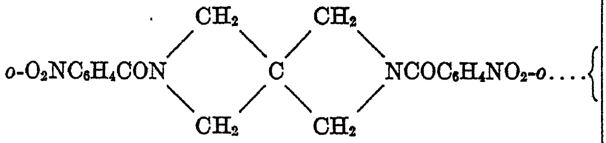
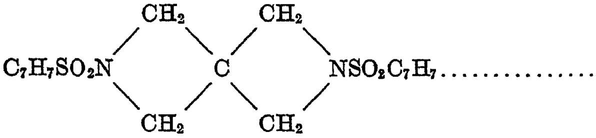
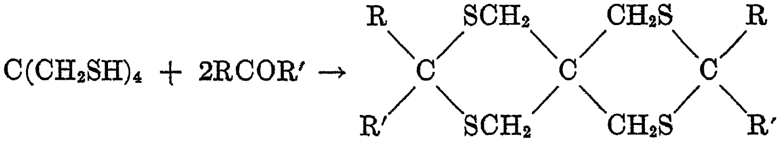
COMPOUND	MELTING POINT °C.	REFERENCE
		(96)
	272	(96)
 tripicrate	212–213 d.	(96)
	285	(96)
	214	(96)
	181	(96)
	208–208.5 d.	(64)
	123–124 d.	(64)

TABLE 17—*Concluded*

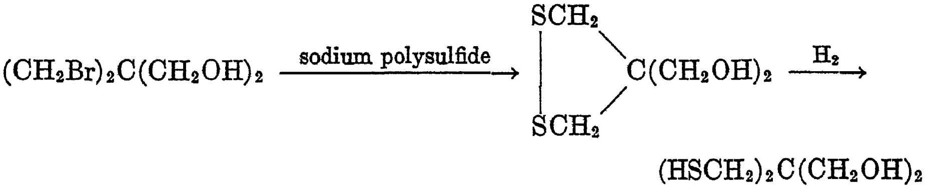
COMPOUND	MELTING POINT	REFERENCE
	°C.	
		(73, 96)
·2HCl	197 275 d.	(73) (96)
·2HBr	196	(73)
Dipicrate	259 243 d.	(73) (96)
	218 232	(96) (73)
	186	(73, 96)

[5.5]undecane; condensation with ketones, such as 1,4-cyclohexanedione, is claimed (86) to give linear polymers suitable for bristles, etc.



The corresponding sulfones of some of these derivatives have been prepared by oxidation with hydrogen peroxide in acetic acid.

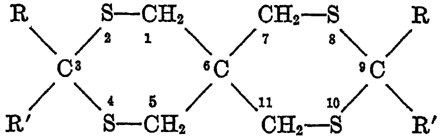
Peppel and Signaigo (120) have reacted sodium polysulfide with pentaerythrityl dibromide to obtain 4,4-dimethylol-1,2-dithiacyclopentane (m.p. 129–130°C.), and by hydrogenation of this compound over a cobalt sulfide catalyst they produced the dithio derivative of pentaerythritol (m.p. 97°C.).



The derivatives of 2,4,8,10-tetrathiaspiro[5.5]undecane which have been prepared from tetrakis(mercaptomethyl)methane are listed in table 18.

TABLE 18

Derivatives of 2,4,8,10-tetrathiaspiro[5.5]undecane (11)



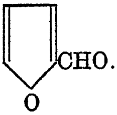
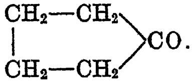
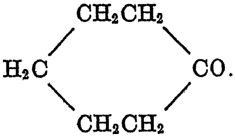
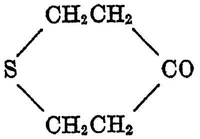
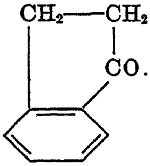
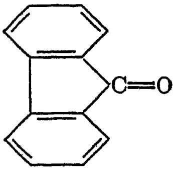
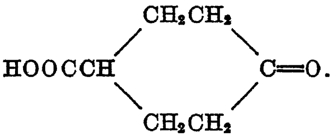
REAGENT	DERIVATIVE	MELTING POINT
		°C.
CH_3CHO	3,9-Dimethyl-	110
$CH_3COCOCH_3$	3,9-Dimethyl-3,9-diacetyl-	164–165.5
	3,9-Difuryl-	132.5–133
CH_3COCH_3	3,3,9,9-Tetramethyl-	192–193
	3,3,9,9-Tetramethyl tetrasulfone	>350
$CH_3COCH_2CH_3$	3,9-Dimethyl-3,9-diethyl-	143–143.5
$(CH_3CH_2)_2CO$	3,3,9,9-Tetraethyl-	118–118.5
	3,3,9,9-Tetraethyl tetrasulfone	>300
$CH_3COC(CH_3)_3$	3,9-Dimethyl-3,9-di-*tert*-butyl-	165–167
$CH_3CH_2COC(CH_3)_3$	3,9-Diethyl-3,9-di-*tert*-butyl-	177–178
	3,9-Bis(tetramethylene)-	212.5–213
	3,9-Bis(tetramethylene) tetrasulfone	>300
	3,9-Bis(pentamethylene)-	206–207
	3,9-Bis(pentamethylene)tetrasulfone	>300
	3,9-Bis(thiodiethylene)-	273
C_6H_5CHO	3,9-Diphenyl-	233–234
p-$CH_3C_6H_4CHO$	3,9-Di-*p*-tolyl-	244–245
Vanillin	3,9-Bis(4-hydroxy-3-methoxyphenyl)-	269–271
Piperonal	3,9-Bis(3,4-methylenedioxyphenyl)	265–267
$C_6H_5CH{=}CHCHO$	3,9-Bis(2-phenylethenyl)-	225–226
$C_6H_5COCH_3$	3,9-Dimethyl-3,9-diphenyl-	184–185
$(C_6H_5)_2CO$	3,3,9,9-Tetraphenyl-	222–223

TABLE 18—*Concluded*

REAGENT	DERIVATIVE	MELTING POINT
		°C.
		258–259
		>300
		

B. Thio ethers, sulfoxides, and sulfones

Thio ethers derived from pentaerythritol have been prepared by Backer and Dijkstra (6) and Backer, Terpstra, and Dijkstra (18) by the reaction of pentaerythrityl tetrabromide with the sodium derivative of the corresponding mercaptan or thiophenol, generally at about 150°C.

$$C(CH_2Br)_4 + 4NaSR \rightarrow C(CH_2SR)_4$$

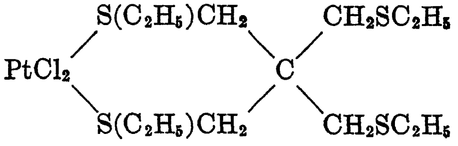
The thio ethers are readily oxidized with hydrogen peroxide in acetic acid to give the corresponding sulfones. The oxidation can also be effected with nitric acid or with potassium permanganate in acetone (7).

$$C(CH_2SR)_4 + 8H_2O_2 \rightarrow C(CH_2SO_2R)_4 + 8H_2O$$

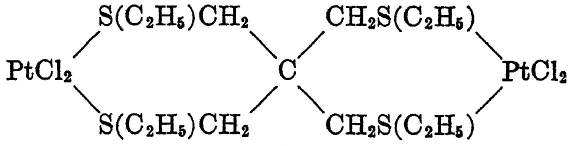
Backer and Dijkstra (8) have prepared the corresponding sulfoxides from the thio ethers by oxidation with the theoretical quantity of hydrogen peroxide or by hydrolysis of their octabromides.

$$\begin{tikzcd} C(CH_2SR)_4 \arrow[rr, "4H_2O_2"] \arrow[dr, "4Br_2"'] & & C(CH_2SOR)_4 \\ & C(CH_2SBr_2R)_4 \arrow[ur, "4H_2O"'] & \end{tikzcd}$$

The thio ethers form addition compounds with mercuric chloride, generally with 2 molecules, although certain thio ethers combine with 4 molecules. Ischugajeff and Iljin (147) have reported that pentaerythrityl tetraethyl thio ether gives two products on reaction with potassium chloroplatinate. In the cold, the compound XLIII is obtained, and if the reactants are heated, a mixture of XLIII with XLIV results.



XLIII

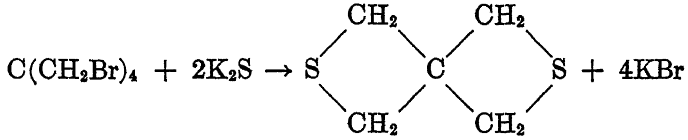


XLIV

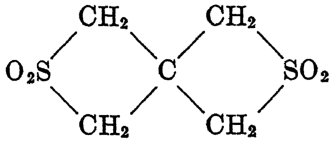
The thio ethers, sulfoxides, and sulfones derived from pentaerythritol, and their derivatives, are listed in table 19.

C. 2,6-Dithiaspiro[3.3]heptane

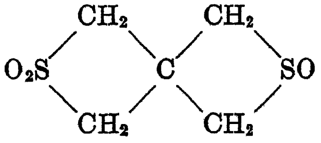
Backer and Keuning (12, 13) have found that 2,6-dithiaspiro[3.3]heptane (XLV) is prepared readily by the action of excess potassium sulfide on pentaerythrityl tetrabromide in alcoholic solution. It has been prepared similarly by Kravets (93).



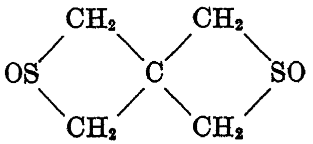
When an insufficiency of potassium sulfide was employed, there was produced only this dithio ether, with no evidence of the monocyclic compound. Theoretically there are five possible oxidation products from this dithio ether, and all have been prepared by Backer and Keuning from it. With potassium permanganate and hydrogen peroxide in excess, the disulfone (XLVI) was readily obtained; with 3 moles of hydrogen peroxide, the sulfoxide-sulfone (XLVII) resulted; and 2 moles of hydrogen peroxide or nitric acid or an excess of chromic acid produced the disulfoxide (XLVIII).



XLVI



XLVII



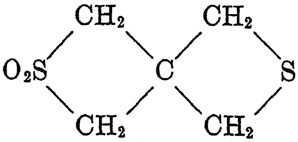
XLVIII

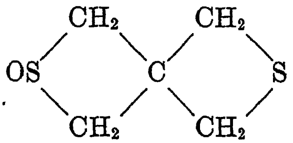
Thio ethers, sulfoxides, and sulfones derived from pentaerythritol

PENTAERYTHRITYL	THIO ETHER (6, 18)		THIO ETHER OCTABROMIDE (8)	THIO ETHER–$HgCl_2$ ADDUCT (8)	SULFOXIDE (8)	SULFONE (7, 8)
	Melting point	Boiling point	Melting point	Melting point	Melting point	Melting point
	°C.	°C.	°C.	°C.	°C.	°C.
Tetramethyl-	−1	209–211/15 mm.	107 d.	$+2HgCl_2$ 143	205	Decomposes >300
Tetraethyl-		218–220/15 mm.*	93 d.	$+2HgCl_2$ 157.5	137	185.5
Tetra-*n*-propyl-		222–225/2 mm.	80 d.	$+2HgCl_2$ 88 $+4HgCl_2$ 141	117	126.5
Tetraisopropyl		192–193/2 mm.	80 d.		165	220.5
Tetraallyl		214–217/2 mm.				
Tetra-*n*-butyl		226–230/2 mm.		$+HgCl_2$ 51 $+2HgCl_2$ 97 $+4HgCl_2$ 149	123	111.5
Tetraisobutyl-		206–208/2 mm.				134
Tetra-*sec*-butyl-		221–223/2 mm.				115
Tetra-*tert*-butyl-	123.6		130 d.	$+2HgCl_2$ Decomposes >300	212	Decomposes >300
Tetra-*n*-amyl-		241–243/2 mm.		$+2HgCl_2$ 84 $+4HgCl_2$ 128	143	83.5
Tetra-*n*-hexyl-		206–208/10^{-5} mm.			159.5	85.5
Tetra-*n*-heptyl-		222–224/10^{-5} mm.				72
Tetra-*n*-octyl-		238–240/10^{-5} mm.				80
Tetra-*n*-nonyl-		251–253/10^{-5} mm.				76
Tetra-*n*-decyl-	19	259–261/10^{-5} mm.				78.8
Tetra-*n*-undecyl-	28					72.5
Tetra-*n*-dodecyl-	35–36					78.3
Tetraphenyl-	86					244
Tetra-*p*-bromophenyl-	110					328
Tetra-*p*-chlorophenyl-	96					276
Tetra-*p*-tolyl-	103					249
Tetrabenzyl-	73					179.5
Tetraphenylethyl-						183

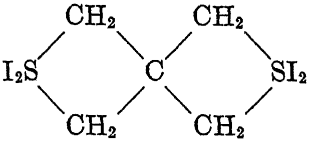
* Reference 147.

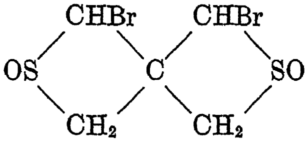
The monosulfone (XLIX) was prepared by the reduction of the sulfoxide-sulfone (XLVII), and the monosulfoxide (L) was prepared by oxidation of the dithio ether with 1 mole of hydrogen peroxide or with chromic acid in acetic acid.


XLIX

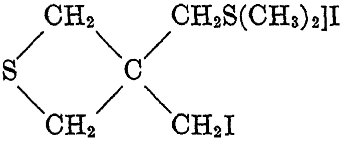

L

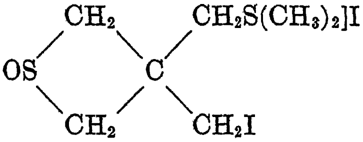
The dithio ether unites with iodine to form the tetraiodide (LI), and reacts with bromine to give a compound which on hydrolysis produces 1,5-dibromo-2,6-dithiaspiro[3.3]heptane-2,6-dioxide (LII). The tetrabromide was obtained as a viscous oil by reaction of the dithio ether with bromine vapor.


LI


LII

The dithio ether combines with mercuric chloride. It unites with methyl iodide to form a compound which is probably LIII, as only one iodine atom is ionized. The monosulfoxide also reacts with 2 molecules of methyl iodide to form a similar compound (LIV).


LIII

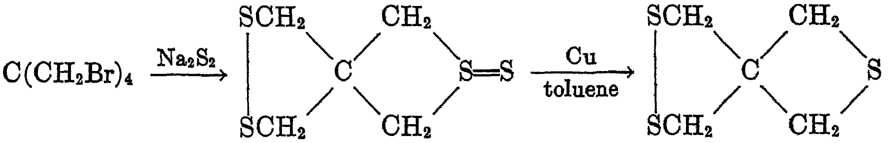

LIV

The disulfoxide forms addition compounds with many salts and it has been resolved through its addition compound with cobalt *d*-camphorsulfonate.

2,6-Dithiaspiro[3.3]heptane and its derivatives are listed in table 20.

D. 2,6,7-Trithiaspiro[3.4]octane

Backer and Evenhuis (9) have shown that by the reaction of sodium or potassium disulfide with pentaerythrityl tetrabromide in boiling ethanol, 2-thio-2,6,7-trithiaspiro[3.4]octane (LV) is produced, and when this is boiled with copper in toluene it is converted to 2,6,7-trithiaspiro[3.4]octane (LVI).


LV LVI

Oxidation of 2-thio-2,6,7-trithiaspiro[3.4]octane with perbenzoic acid gave 2,6,7-trithiaspiro[3.4]octane-2,2,6,6-tetraoxide (LVII), and when hydrogen

TABLE 20

2,6-Dithiaspiro[3.3]heptane and its derivatives

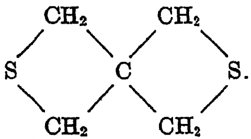
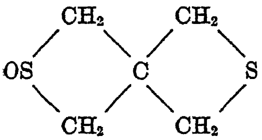
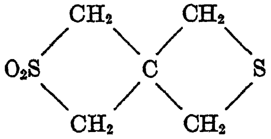
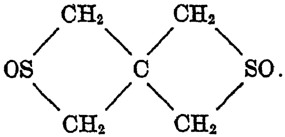
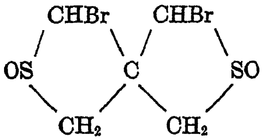
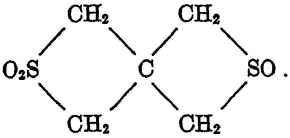
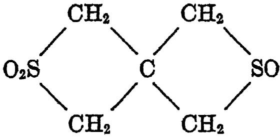
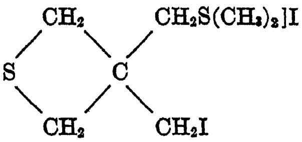
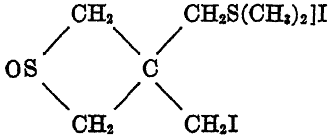
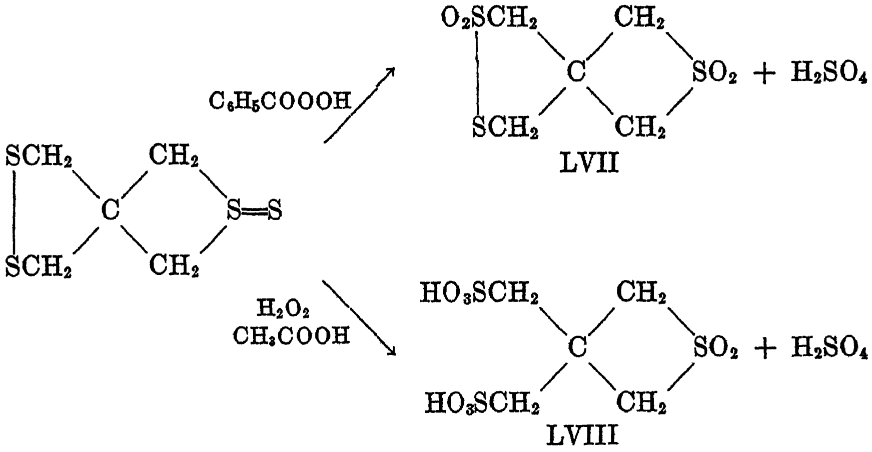
COMPOUND	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
	31.5		(12)
		108–109/16 mm.	(93)
		116–118/15 mm.	
+ $2HgCl_2$	Decomposes		(12)
+ $2Br_2$		Viscous oil	(13)
+ $2I_2$	Decomposes about 100		(12)
	81.5		(12)
+ $1.5HgCl_2$	Decomposes		(12)
	116.5		(12)
+ $HgCl_2$	177–178		(12)
	146		(12)
+ $2HgCl_2$	185 d.		(12)
+ $0.5CuCl_2$			(13)
+ $CuCl_2$			(13)
+ $CaCl_2$			(13)
+ $MnCl_2$			(13)
+ $0.5NiCl_2$			(13)
+ $0.5CoCl_2$			(13)
+ $1.33CdCl_2$			(13)
+ H_2PtCl_6			(13)
	126.5		(12)
+ $0.5HgCl_2$	120 d.		(13)

TABLE 20—*Concluded*

COMPOUND	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
............	156		(12)
+ $HgCl_2$...........	186–187 d.		(12)
..........	244.5 136–137		(12) (93)
..........	143 d. 135		(12, 13, 93)
........	133–134		(13)

peroxide in acetic acid was used as the oxidizing agent 1-thia-3,3-disulfodimethylcyclobutane-1,1-dioxide (LVIII) was produced; a molecule of sulfuric acid was also isolated from each oxidation.



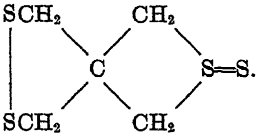
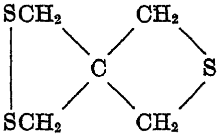
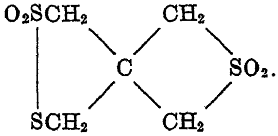
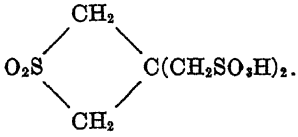
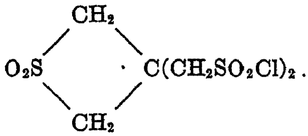
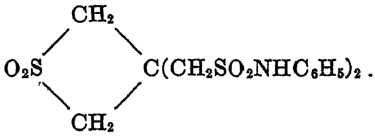
Derivatives of 2,6,7-trithiaspiro[3.4]octane which have been prepared from pentaerythritol are listed in table 21.

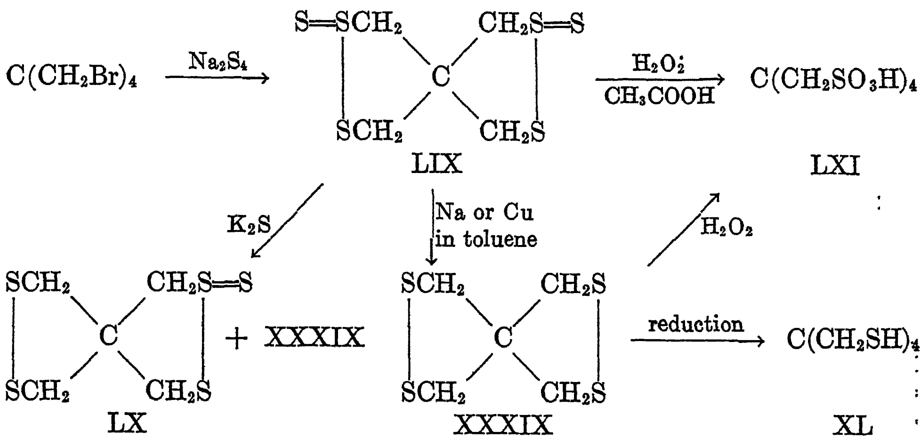
E. 2,3,7,8-Tetrathiaspiro[4.4]nonane

The reaction of pentaerythrityl tetrabromide with sodium tetrasulfide in boiling alcohol has also been examined by Backer and Evenhuis (10), and a product has been isolated which is probably 2,7-dithio-2,3,7,8-tetrathiaspiro[4.4]nonane (LIX). Reaction of this hexasulfide with sodium or copper in boiling toluene produced 2,3,7,8-tetrathiaspiro[4.4]nonane (XXXIX), and reaction with potassium sulfide in boiling alcohol gave 2-thio-2,3,7,8-tetrathiaspiro[4.4]nonane (LX), together with some of the tetrasulfide (XXXIX).

TABLE 21

Derivatives of 2,6,7-trithiaspiro[3.4]octane

COMPOUND	MELTING POINT	REFERENCE
	°C.	
	78.5	(9)
+ $HgCl_2$		(9)
+ $HgBr_2$		(9)
	55.5–56.5	(9)
	257 d.	(9)
		(9)
	144–146 d.	(9)
	200–202	(9)

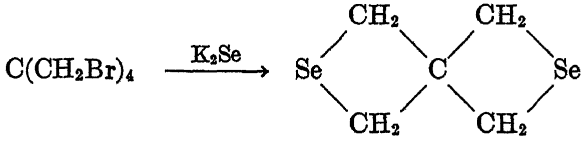


Reduction of the tetrasulfide (XXXIX) with sodium in liquid ammonia (11) produced tetrakis(mercaptomethyl)methane (XL) (see page 182), and oxidation of the hexasulfide (LIX) or the tetrasulfide (XXXIX) with hydrogen peroxide in acetic acid gave tetramethylmethanetetrasulfonic acid (LXI).

Derivatives of 2,3,7,8-tetrathiaspiro[4.4]nonane which have been prepared from pentaerythritol are shown in table 22.

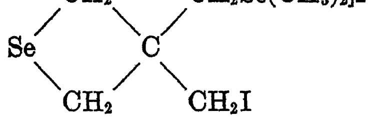
XI. 2,6-DISELENASPIRO[3.3]HEPTANE

By the reaction of potassium selenide with pentaerythrityl tetrabromide in an inert atmosphere, Backer and Winter (19) have prepared 2,6-diselenaspiro[3.3]-heptane (LXII).



LXII

This substance is readily oxidizable, and forms an addition compound with mercuric chloride; its 2,2,6,6-tetraiodo derivative is unstable. Reaction with 2 molecules of methyl iodide produces 3-iodomethyl-3-methylselenolmethyl-1-selenacyclobutane methiodide (LXIII).



LXIII

The derivatives of 2,6-diselenaspiro[3.3]heptane which have been prepared from pentaerythritol are listed in table 23.

XII. COMPOUNDS WITH ARSENIC AND BORON

Englund (51) suggested that reaction took place between pentaerythritol and arsenic derivatives, because of the observed increased solubility of the arsenic

TABLE 22

2,3,7,8-Tetrathiaspiro[4.4]nonane derivatives

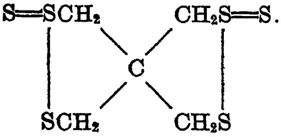
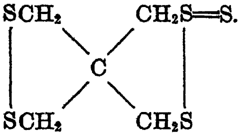
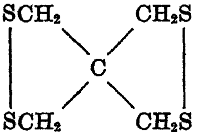
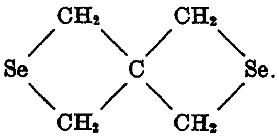
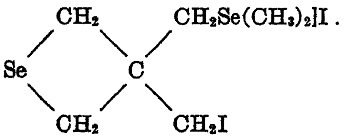
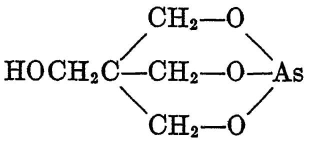
COMPOUND	MELTING POINT °C.	REFERENCE
	182–184	(10)
	117.5–118	(10)
	80–80.5	(10)
+ $HgCl_2$	132	
+ $HgBr_2$	127–127.5	
$C(CH_2SO_3H)_4$		(10)
$C(CH_2SO_2Cl)_4$	217 d.	(10)

TABLE 23

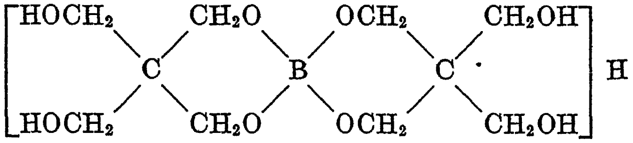
Derivatives of 2,6-diselenaspiro[3.3]heptane

COMPOUND	MELTING POINT °C.	REFERENCE
	67	(19)
+ $2HgCl_2$		(19)
+ $2I_2$		(19)
	112–113	(19)
Picrate	113–113.5	

derivative in glacial acetic acid when pentaerythritol was present. By heating together pentaerythritol and arsenious oxide (52) he isolated a crystalline compound $C_5H_9O_4As$, m.p. 102–103°C., probably having the following structure:



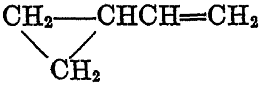
Orthner and Freyss (119) have examined the specific conductivity of boric acid in the presence of pentaerythritol and its derivatives. No increase in conductivity was observed by the addition of the monoisopropylidene derivative of pentaerythritol, pentaerythrityl dimethyl ether, or pentaerythrityl dibenzoate, but pentaerythritol itself was found to cause an increase in conductivity and this was ascribed to the formation of the compound:



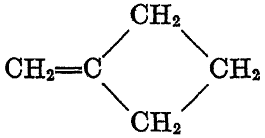
XIII. SPIRANES

The products of the debromination of pentaerythrityl tetrabromide have attracted a considerable number of workers, and there are many conflicting statements in their publications.

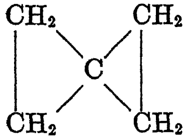
Gustavson (78) first debrominated pentaerythrityl tetrabromide with zinc. He assigned to the reduction product the structure of vinyltrimethylene (LXIV), although later (79) he suggested that methylenecyclobutane (LXV) was possibly more likely. Fecht (56) concluded that the product was spiropentane (LXVI).



LXIV

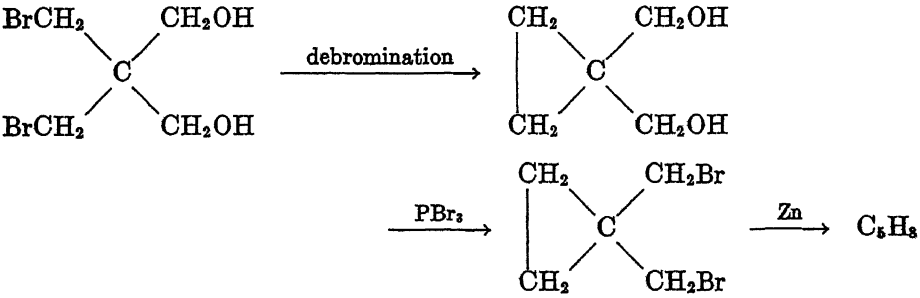


LXV



LXVI

Demjanov (45) favored the methylenecyclobutane structure and Zelinski (157), who did his debromination in two stages, concluded that the spirocyclane structure would more nearly account for the chemical reactions and synthesis of the compound.



Favorski and Batalin (55) decided that Gustavson's "vinyl trimethylene" was methylenecyclobutane, and Filipov (61) said that the reduction product was a mixture of methylenecyclobutane and methylcyclobutene.

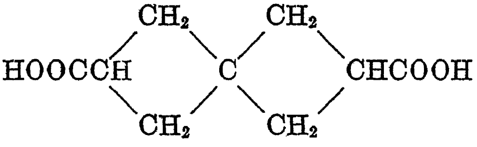
Merezhkovskii (106) repeated Fecht's work and concluded that the allocation of the spirocyclane structure was not justified by the evidence, and Demjanov and Dojarenko (46) in 1922 preferred methylenecyclobutane. Ingold in 1923 (87) was unable to isolate any spiropentane from the reduction product. Rogowski (129) interpreted the results of an electron diffraction study on the reduction product as being consistent with the spiropentane structure.

Williams (154) has prepared cyclobutane derivatives by the debromination of pentaerythrityl tetrabromide with zinc and it is recorded (153) that Whitmore and Philips, by debromination with zinc, obtained a mixture shown by ozonolysis to consist of methylenecyclobutane and 2-methyl-1-butene with no evidence of other compounds.

Bauer and Beach (23) made an electron diffraction study of the high-boiling fraction obtained by Whitmore and Williams and concluded that it was methylenecyclobutane and not spiropentane. Murray and Stevenson (110) in 1944, by Raman spectroscopic examination, found that the product of the debromination of pentaerythrityl tetrabromide with zinc in aqueous methanol consisted of methylenecyclobutane, 2-methyl-1-butene and a small quantity of a compound considered to be spiropentane. When reduction was carried out with zinc in molten acetamide in the presence of sodium iodide and sodium carbonate, they obtained the same mixture, but with the spiropentane fraction in 40 per cent yield. It is recorded that the spiropentane fraction was chemically stable. Donohue, Humphrey, and Schomaker (47) have confirmed the structure of this compound as spiropentane by electron diffraction studies. Slabey (142) carried out a debromination of pentaerythrityl tetrabromide in ethanol with zinc in the presence of sodium iodide and sodium carbonate. He obtained a higher yield of hydrocarbon products (78–89 per cent) than Murray and Stevenson, and these were found to consist of methylenecyclobutane (54–58 per cent), spiropentane (24–28 per cent), 2-methyl-1-butene (13–18 per cent), and 1,1-dimethylcyclopropane (1–3 per cent).

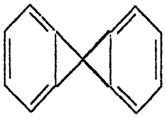
Shand, Schomaker, and Fischer (138) have carried out electron diffraction studies of methylenecyclobutane which they isolated from the debromination of pentaerythrityl tetrabromide. From the reaction product they could not isolate any methylcyclobutene.

Fecht (56) reported the preparation of spiro[3.3]heptane-2,5-dicarboxylic acid (LXVII) and the corresponding 2,2,5,5-tetracarboxylic acid from pentaerythrityl tetrabromide and malonic ester. The dicarboxylic acid has also been prepared by Backer and Schurink (15) and has been resolved by them.



LXVII

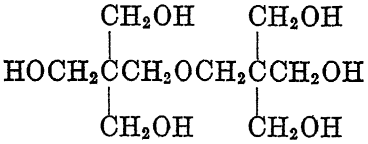
Fecht (56) caused benzene, aluminum chloride, and pentaerythrityl tetrabromide to react, and obtained two hydrocarbons in poor yield. The structure LXVIII was not ascribed to either.



LXVIII

XIV. DIPENTAERYTHRITOL

Dipentaerythritol (LXIX) is the ether derived from 2 molecules of pentaerythritol by elimination of 1 molecule of water.



$$\begin{array}{c} \quad CH_2OH \qquad CH_2OH \\ HOCH_2\overset{|}{\underset{|}{C}}CH_2OCH_2\overset{|}{\underset{|}{C}}CH_2OH \\ \quad CH_2OH \qquad CH_2OH \end{array}$$

LXIX

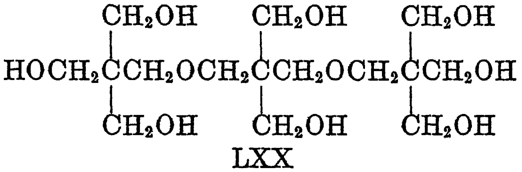
There is no record of its synthesis from pentaerythritol, and its only known preparation is as a by-product in the manufacture of pentaerythritol. It is present in varying amounts in commercial pentaerythritol, generally of the order of 5 per cent or less.

The separation of dipentaerythritol from large quantities of pentaerythritol by crystallization from water is difficult on account of their similar solubilities, and also on account of the formation of double compounds. For example, the double compound $(CH_2OH)_3CCH_2OCH_2C(CH_2OH)_3 \cdot 4C(CH_2OH)_4$, m.p. 185–190°C., crystallizes unchanged from hot water, and is not split into its components below 108°C. (156). It has been claimed (99) that a considerable separation of dipentaerythritol from pentaerythritol can be effected by applying a wet-sieving or scouring process to the crude pentaerythritol synthesis product, because of differing particle sizes. Bried (37) has claimed that by altering the conditions of the pentaerythritol synthesis, a product can be obtained which contains as much as 35–40 per cent of dipentaerythritol. Friederich and Brün (62) have prepared pure dipentaerythritol by separating a mixture of pentaerythritol tetranitrate and dipentaerythritol hexanitrate by their differing solubilities in acetone, followed by saponification. The chromatographic separation of a small amount of dipentaerythritol from a large amount of pentaerythritol has been reported by Lew, Wolfrom, and Goepp (94).

A few derivatives of dipentaerythritol have been prepared, and these are listed in table 24. Friederich and Brün (62) record that dipentaerythritol hexaformate eliminated carbon monoxide at 270°C. to give dipentaerythritol almost quantitatively, and that the hexatrityl ether of dipentaerythritol is readily decomposed by water. From the oxidation of dipentaerythritol with nitric acid they isolated a polymerization product of diglycolic aldehyde, $O(CH_2CHO)_2$.

XV. HIGHER POLYPENTAERYTHRITOLS

Burrell (43) has stated that tripentaerythritol, m.p. 242–248°C., has been isolated from the pentaerythritol synthesis by-products and that its structure has been proved to be LXX, but so far this work has not been published.



$$\mathrm{HOCH_2}\underset{\mathrm{CH_2OH}}{\underset{|}{\overset{\mathrm{CH_2OH}}{\overset{|}{\mathrm{C}}}}}\mathrm{CH_2OCH_2}\underset{\mathrm{CH_2OH}}{\underset{|}{\overset{\mathrm{CH_2OH}}{\overset{|}{\mathrm{C}}}}}\mathrm{CH_2OCH_2}\underset{\mathrm{CH_2OH}}{\underset{|}{\overset{\mathrm{CH_2OH}}{\overset{|}{\mathrm{C}}}}}\mathrm{CH_2OH}$$

LXX

TABLE 24

Derivatives of dipentaerythritol

COMPOUND	MELTING POINT	BOILING POINT	REFERENCE
	°C.	°C.	
Dipentaerythritol	221		(62)
Dipentaerythritol hexaformate	56		(62)
Dipentaerythritol hexaacetate	73		(62)
Dipentaerythritol hexapropionate		240–250/2 mm.	(158)
Dipentaerythritol triacetate tripropionate		Viscous liquid	(22)
Dipentaerythritol hexabutyrate	15–20		(158)
Dipentaerythritol hexabenzoate	183		(62)
Dipentaerythritol hexanitrate	75		(62)
Dipentaerythritol diiodohydrin	106–107		(62)
Dipentaerythritol hexabutyl ether	173		(62)
Dipentaerythritol allyl ethers:			
4.6 Allyl groups		174/0.3 mm.	(115)
Hexaallyl		184–186/1 mm.	(115)
Dipentaerythritol methallyl ethers:			
4.6 Methallyl groups		200–205/0.8 mm.	
Hexamethallyl		183–185/0.3 mm.	(115)

Wyler (155) has nitrated tripentaerythritol and obtained the octanitrate, m.p. 82–84°C., which is claimed to be a useful explosive.

A mixture of polypentaerythritols of m.p. 230–240°C. which is obtained from the pentaerythritol by-products approximates closely to tripentaerythritol and has been named pleopentaerythritol. It is considered by Burrell (43) to be a mixture of di- and tri-pentaerythritols with probably some tetrapentaerythritol.

XVI. REFERENCES

(1) Adam, N. K., and Dyer, J. W. W.: Proc. Roy. Soc. (London) **A106**, 694 (1924).
(2) Alexander, A. E.: Proc. Roy. Soc. (London) **A179**, 486 (1942).
(3) Alphen, J. van: Rec. trav. chim. **57**, 265 (1938).
(4) Apel, M., and Tollens, B.: Ann. **289**, 36 (1896).
(5) Backer, H. J., and Dijken, G.: Rec. trav. chim. **55**, 22 (1936).

(6) Backer, H. J., and Dijkstra, N. D.: Rec. trav. chim. **51,** 289 (1932).
(7) Backer, H. J., and Dijkstra, N. D.: Rec. trav. chim. **51,** 1173 (1932).
(8) Backer, H. J., and Dijkstra, N. D.: Rec. trav. chim. **52,** 701 (1933).
(9) Backer, H. J., and Evenhuis, N.: Rec. trav. chim. **56,** 129 (1937).
(10) Backer, H. J., and Evenhuis, N.: Rec. trav. chim. **56,** 174 (1937).
(11) Backer, H. J., and Evenhuis, N.: Rec. trav. chim. **56,** 681 (1937).
(12) Backer, H. J., and Keuning, K. J.: Rec. trav. chim. **52,** 499 (1933).
(13) Backer, H. J., and Keuning, K. J.: Rec trav. chim. **53,** 798 (1934).
(14) Backer, H. J., and Keuning, K. J.: Rec. trav. chim. **53,** 812 (1934).
(15) Backer, H. J., and Schurink, H. B. J.: Rec. trav. chim. **50,** 921 (1931).
(16) Backer, H. J., and Schurink, H. B. J.: Rec. trav. chim. **50,** 1066 (1931).
(17) Backer, H. J., and Strating, J.: Rec. trav. chim. **62,** 815 (1943).
(18) Backer, H. J., Terpstra, P., and Dijkstra, N. D.: Rec. trav. chim. **51,** 1166 (1932).
(19) Backer, H. J., and Winter, H. J.: Rec. trav. chim. **56,** 492 (1937).
(20) Baltzly, R., and Buck, J. S.: J. Am. Chem. Soc. **63,** 2022 (1941).
(21) Barbiere, J., and Matti, J.: Bull. soc. chim. [5] **5,** 1565 (1938).
(22) Barth, R. H., and Burrell, H. (to Heyden Chemical Corp.): U. S. patent 2,356,745 (1944).
(23) Bauer, S. H., and Beach, J. Y.: J. Am. Chem. Soc. **64,** 1142 (1942).
(24) Beintema, J., Terpstra, P., and Weerden, W. J.: Rec. trav. chim. **54,** 627 (1935).
(25) Bennett, H.: *Commercial Waxes, Natural and Synthetic*, p. 111. Chapman and Hall, Ltd., London (1944).
(26) Beyaert, M., and Govaert, F.: Proc. Acad. Sci. Amsterdam **42,** 776 (1939); Chem. Abstracts **34,** 5414 (1940).
(27) Beyaert, M., and Hansens, M.: Natuurw. Tijdschr. (Belg.) **22,** 249 (1940); Chem. Abstracts **37,** 5373 (1943).
(28) Bincer, H., and Hess, K.: Ber. **61B,** 537 (1928).
(29) Blagonravova, A. A., and Drinberg, A. Ya.: J. Applied Chem. (U. S. S. R.) **11,** 1642; Chemical Abstracts **33,** 5805 (1939).
(30) Böeseken, J., with Schaefer, M. G., and Hermans, P.: Rec. trav. chim. **41,** 722 (1922):
(31) Böeseken, J., and Felix, B. B. C.: Ber. **61B,** 787 (1928).
(32) Böeseken, J., and Felix, B. B. C.: Ber. **61B,** 1855 (1928).
(33) Böeseken, J., and Felix, B. B. C.: Ber. **62B,** 1310 (1929).
(34) Boissonou, C. J. (to Shell Development Co.): U. S. patent 2,369,429; Chem. Abstracts **40,** 164 (1946).
(35) Bougault, J.: Compt. rend. **123,** 187 (1896).
(36) Bowman, P. I., Barth, R. H., and Burrell, H. (to Heyden Chemical Corp.): U. S. patent 2,401,743 (1946).
(37) Bried, E. A. (to Hercules Powder Co.): U. S. patent 2,325,589 (1944).
(38) British Celanese Ltd.: British patent 579,179 (1946).
(39) Brown, K. R. (to Atlas Powder Co.): U. S. patent 2,357,078; Chem. Abstracts **39,** 386 (1945).
(40) Bruson, H. (to The Resinous Products & Chemical Co.): U. S. patent 2,359,708 (1944); 2,372,808 (1945); 2,401,607 (1946).
(41) Bruson, H. (to The Resinous Products & Chemical Co.): U. S. patent 2,383,443 (1945).
(42) Burke, C. E.: (to E. I. du Pont de Nemours & Co.): U. S. patents 1,774,500 (1930), and 1,859,913 (1932).
(43) Burrell, H.: Ind. Eng. Chem. **37,** 86 (1945).
(44) Contardi, A., and Ciocca, B.: Rend. ist. lombardo sci. **69,** 1057 (1936); Chem. Abstracts **33,** 4583 (1939).
(45) Demjanow, N. J.: Ber. **41,** 915 (1908).
(46) Demjanow, N. J., and Dojarenko, M.: Ber. **55B,** 2727 (1922).

(47) Donohue, J., Humphrey, G. L., and Schomaker, V.: J. Am. Chem. Soc. **67,** 332 (1945).

(48) Dostrovsky, I., Hughes, E. D., and Ingold, C. K.: J. Chem. Soc. **1946,** 187.

(49) Drinberg, A. Ya., and Blagonravova, A. A.: Org. Chem. Ind. (U. S. S. R.) **7,** 388 (1940); Chem. Abstracts **35,** 3966 (1941).

(50) Eidebenz, E., and Depner, M.: Arch. Pharm. **280,** 227 (1942); Chem. Abstracts **37,** 2715 (1943).

(51) Englund, B.: Svensk. Kem. Tids. **40,** 278 (1928); Chem. Abstracts **23,** 2429 (1929).

(52) Englund, B.: J. prakt. Chem. **124,** 191 (1930).

(53) Fairbourne, A., and Woodley, J. W.: J. Chem. Soc. **1926,** 3240.

(54) Farlow, M. W., and Signaigo, F. K. (to E. I. du Pont de Nemours & Co.): U. S. patent 2,402,614 (1946); Chem. Abstracts **40,** 5763 (1946).

(55) Favorski, A., and Batalin, W.: Ber. **47,** 1648 (1914).

(56) Fecht, H.: Ber. **40,** 3883 (1907).

(57) Fedotova, O. Ya.: J. Chem. Ind. (U. S. S. R.) **18,** No. 3, 28 (1941); Chem. Abstracts **38,** 3636 (1944).

(58) Filbert, W. F. (to E. I. du Pont de Nemours & Co.): U. S. patent 2,358,697 (1944).

(59) Fourneau, E., Matti, J., and Dunant, Y.: Bull. soc. chim. [5] **4,** 1155 (1937).

(60) Filipov, O.: J. Russ. Phys. Chem. Soc. **46,** 1141 (1914); Chem. Zentr. **1915, I,** 1057.

(61) Filipov, O.: J. prakt. Chem. **93,** 162 (1916).

(62) Friederich, W., and Brun, W.: Ber. **63B,** 2681 (1930).

(63) Gibson, G. M., Harley-Mason, J., Litherland, A., and Mann, F. G.: J. Chem. Soc. **1942,** 163.

(64) Gibson, G. M., and Mann, F. G.: J. Chem. Soc. **1942,** 175.

(65) Giebe, E., and Scheibe, A.: Z. Physik **33,** 760 (1925).

(66) Glattfeld, J. W. E., and Schneider, J. M.: J. Am. Chem. Soc **60,** 415 (1938).

(67) Govaert, F.: Proc. Acad. Sci. Amsterdam **37,** 156 (1934); Chem. Abstracts **28,** 4038 (1934).

(68) Govaert, F., and Beyaert, M.: Natuurw. Tijdschr. (Belg.) **21,** 29 (1939); Chem. Abstracts **33,** 9284 (1939).

(69) Govaert, F., and Beyaert, M.: Proc. Acad. Sci. Amsterdam **42,** 637 (1939); Chem. Abstracts **34,** 2790 (1940).

(70) Govaert, F., and Beyaert, M.: Proc. Acad. Sci. Amsterdam **42,** 641 (1939); Chem. Abstracts **34,** 2790 (1940).

(71) Govaert, F., and Beyaert, M.: Proc. Acad. Sci. Amsterdam **42,** 790 (1939); Chem. Abstracts **34,** 5415 (1940).

(72) Govaert, F., and Beyaert, M.: Natuurw. Tijdschr. (Belg.) **22,** 73 (1940); Brit. Chem. Abstracts **1946, AII,** 632.

(73) Govaert, F., and Beyaert, M.: Bull. soc. chim. Belg. **55,** 106 (1946).

(74) Govaert, F., and Cazier, J.: Natuurw. Tijdschr. (Belg.) **23,** 149 (1942); Chem. Abstracts **37,** 6245 (1943).

(75) Govaert, F., and Cazier, J.: Bull. soc. chim. Belg. **54,** 43 (1945).

(76) Govaert, F., and Hansens, M.: Natuurw. Tijdschr. (Belg.) **21,** 215 (1940); Chem. Abstracts **34,** 3680 (1940).

(77) Govaert, F., Hansens, M , and Beyaert, M : Versl. Gewone Vergader Afdeel Natuurk. **52,** 135 (1943); Chem. Abstracts **38,** 5201 (1944).

(78) Gustavson, G.: J. prakt. Chem. **54,** 97 (1896); Compt. rend. **123,** 242 (1896).

(79) Gustavson, G., and Bulatoff, H.: J. prakt. Chem. **56,** 93 (1897).

(80) Gustavson, G., and Popper, O.: J. prakt. Chem. **56,** 95 (1897).

(81) Haga, H., and Jaeger, F. M.: Proc. Akad. Wetenschappen Amsterdam **18,** 1350 (1916).

(82) Hansens, M., and Beyaert, M.: Natuurw. Tijdschr. (Belg.) **22,** 263 (1940); Chem. Abstracts **37,** 5374 (1943).

(83) Hendricks, S. B.: Z. Krist. **66,** 131 (1927).

(84) Holt, H. S. (to E. I. du Pont de Nemours & Co.): U. S. patent 2,031,603 (1936).

(85) Huggins, M. L., and Hendricks, S. B.: J. Am. Chem. Soc. **48,** 164 (1926).
(86) Imperial Chemical Industries Ltd.: British patent 577,205.
(87) Ingold, C. K.: J. Chem. Soc. **123,** 1706 (1923).
(88) Johnston, F. L. (to Shell Development Co.): U. S. patent 2,371,333 (1945); Chem. Abstracts **39,** 5470 (1945).
(89) Kenner, J.: Ber. **61B,** 2470 (1928).
(90) Knaggs, I. E.: Proc. Roy. Soc. (London) **A122,** 69 (1929).
(91) Kraft, M. Ya.: J. Chem. Ind. (Moscow) **8,** 507 (1931); Chem. Abstracts **25,** 5114 (1931).
(92) Kraft, M. Ya.: J. Gen. Chem. (U. S. S. R.) **16,** 677 (1946); Chem. Abstracts **41,** 1207 (1947).
(93) Kravets, V. P.: J. Gen. Chem. (U. S. S. R.) **16,** 627 (1946); Chem. Abstracts **41,** 1653 (1947).
(94) Lew, B. W., Wolfrom, M. L., and Goepp, R. M.: J. Am. Chem. Soc. **68,** 1449 (1946).
(95) Liebisch, T.: *Grundriss der phys. Kryst.*, p. 141. Veit and Company, Leipzig (1896).
(96) Litherland, A., and Mann, F. G.: J. Chem. Soc. **1938,** 1588.
(97) Llewellyn, F. J., Cox, E. G., and Goodwin, T. H.: J. Chem. Soc. **1937,** 883.
(98) Lonsdale, K.: Phil. Mag. [7] **6,** 433 (1928).
(99) Lonza Elektrizitätswerke und Chemische Fabriken A.-G.: British patents 440,691 (1941); 535,309 (1941).
(100) Mann, F. G., and Litherland, A.: Nature **141,** 789 (1938).
(101) Mann, F. G., and Watson, J.: J. Chem. Soc. **1943,** 606.
(102) Margaillan, L., and Savary, P.: Bull. soc. chim. France **1947,** 188.
(103) Mark, H., and Susich, G. v.: Z. Krist. **69,** 105 (1928).
(104) Mark, H., and Weissenberg, K.: Z. Physik **17,** 301 (1923).
(105) Martin, J.: Neues Jahrb Mineral. Geol. **7,** 1 (1890).
(106) Merezhkovskii, I. B. K.: J. Russ. Phys. Chem. Soc. **46,** 517; Chem. Abstracts **8,** 3187 (1914).
(107) Mkhitaryan, V. G.: J. Gen. Chem. (U. S. S. R.) **9,** 1923 (1939); Chem. Abstracts **34,** 4381 (1940).
(108) Möller, H., and Reis, A.: Z. Krist. **68,** 385 (1928).
(109) Mooradian, A., and Cloke, J. B.: J. Am. Chem. Soc. **67,** 942 (1945).
(110) Murray, M. J., and Stevenson, E. H.: J. Am. Chem. Soc. **66,** 314, 812 (1944).
(111) Muskat, I. E., and Strain, F. (to Pittsburgh Plate Glass Co.): U. S. patent 2,384,115 (1945), Chem. Abstracts **40,** 2457 (1946); U. S. patent 2,385,931 (1945), Chem. Abstracts **40,** 2461 (1946).
(112) Nayar, P. G. N.: Proc. Indian Acad. Sci. **7A,** 251 (1938).
(113) Nieuwland, J. A., Vogt, R. R., and Foohey, W. L.: J. Am. Chem. Soc. **52,** 1018 (1930).
(114) Nichols, P. L., Hamilton, R. M., Smith, L. T., and Yanovsky, E.: Paint Ind. Mag. **60,** 84, 86, 88, 90 (1945); Chem. Abstracts **39,** 2428 (1945).
(115) Nichols, P. L., Wrigley, A. N., and Yanovsky, E.: J. Am. Chem. Soc. **68,** 2020 (1946).
(116) Nichols, P. L., and Yanovsky, E.: J. Am. Chem. Soc. **67,** 46 (1945).
(117) Nitta, I.: Bull. Chem. Soc. Japan **1,** 62 (1926).
(118) Orthner, L.: Ber. **61B,** 116 (1928).
(119) Orthner, L., and Freyss, G.: Ann. **484,** 131 (1930).
(120) Peppel, W. J., and Signaigo, F. K. (to E. I. du Pont de Nemours & Co.): U. S. patent 2,402,665 (1946); Chem. Abstracts **40,** 5762 (1946).
(121) Perkin, W. H., and Simonsen, J. L.: J. Chem. Soc. **87,** 855 (1905).
(122) Pfeiffer, P., and Backes, P.: Ber. **61B,** 434 (1928).
(123) E. I. du Pont de Nemours: British patent 436,885.
(124) Radulescu, D., and Tanasescu, I.: Bul. soc. stiinte Cluj **1,** 192 (1922); Chem. Abstracts **18,** 1286 (1924).
(125) Rapoport, H.: J. Am. Chem. Soc. **68,** 341 (1946).

(126) Rave, P., and Tollens, B.: Ann. **276,** 58 (1893).

(127) Read, J.: J. Chem. Soc. **101,** 2090 (1912).

(128) Reis, A.: Ber. **59B,** 1543 (1926).

(129) Rogowski, F.: Ber. **72B,** 2021 (1939).

(130) Romburgh, P. van: Proc. Koninkl. Akad. Wetenschappen Amsterdam **10,** 166 (1907); Brit. Chem. Abstracts **92, I,** 1011 (1907); Z. physik. Chem. **130,** 334 (1927).

(131) Rost, A., and Richter, K. (Westfälisch-Anhaltische Sprengstoff A.-G. Chem. Fab.): German patent 722,554 (1942); Chem. Abstracts **37,** 5081 (1943).

(132) Rost, A., and Richter, K. (Westfälisch-Anhaltische Sprengstoff A.-G. Chem. Fab.): German patent 723,497 (1942); Chem. Abstracts **37,** 5418 (1943).

(133) Savary, P.: Bull. mat. grasses inst. colonial Marseille **30,** 84 (1946); Chem. Abstracts **40,** 6853 (1946); Bull. soc. chim. France **1947,** 258.

(134) Schulz, M., and Tollens, B.: Ber. **27,** 1892 (1894); Ann. **289,** 20 (1896).

(135) Schurink, H. B.: *Organic Syntheses,* Collective Vol. II, p. 476. Chapman and Hall, Ltd., London (1943).

(136) Scott, N. D. (to E. I. du Pont de Nemours & Co.): U. S. patent 2,027,000 (1936); U. S. patent 2,183,847 (1939).

(137) Semenzov, A.: Ber. **62B,** 514 (1929).

(138) Shand, W., Schomaker, V., and Fischer, J. R.: J. Am. Chem. Soc **66,** 636 (1944)

(139) Sidgwick, N. V., and Bowen, E. J.: Ann. Repts. Progress Chem. (Chem. Soc. London) **28,** 395 (1931).

(140) Skrabal, A., and Kalpasanoff, S.: Ber. **61B,** 55 (1928).

(141) Skrabal, A., and Zlatewa, M.: Z. physik Chem. **119,** 305 (1926).

(142) Slabey, V. A.: Natl. Advisory Comm. Aeronaut. Tech. Note No. **1023** (1946); Chem. Abstracts **40,** 3729 (1946); J. Am. Chem. Soc. **68,** 1335 (1946).

(143) Tanasescu, I.: Bul. soc. stiinte Cluj **2,** 111; Chem. Abstracts **19,** 2932 (1925).

(144) Tanasescu, I., and Iliescu, I.: Bull. soc. chim. [5] **5,** 1446 (1938).

(145) Tanasescu, I., and Macovski, E.: Bull. soc. chim. [4] **51,** 1371 (1932).

(146) Tollens, B., and Wigand, P.: Ann. **265,** 316 (1891).

(147) Tschugajeff, L., and Iljin, S.: Z. anorg. allgem. Chem. **135,** 143 (1924).

(148) Valentin, F.: Collection Czechoslov. Chem. Commun. **3,** 499 (1931); Chem. Abstracts **26,** 1578 (1932).

(149) Vignon, L., and Gerin, F.: Compt. rend. **133,** 590 (1901).

(150) Weissenberg, K.: Ber. **59B,** 1526 (1926).

(151) Westenbrink, H. G., and Melle, F. A. van: Z. Krist. **64,** 548 (1926).

(152) Westfälisch-Anhaltische Sprengstoffe A.-G. Chem. Fab.: German patents 638,432; 638,433; Chem. Abstracts **31,** 1212 (1937).

(153) Whitmore, F. C., and Williams, P. H.: J. Am. Chem. Soc. **64,** 1145 (footnote 5) (1942).

(154) Williams, P.: Univ. Microfilms, Pub. No. 360 (1941); Chem. Abstracts **36,** 3157 (1942).

(155) Wyler, J. A. (to Trojan Powder Co.): U. S. patent 2,389,228 (1945).

(156) Wyler, J. A. (to Trojan Powder Co.): U. S. patents 2,270,839 (1942); 2,288,929 (1942). Wyler, J. A., and Wernett, E. A. (to Trojan Powder Co.): U. S. patents 2,251,236 (1941); 2,299,048 (1942).

(157) Zelinski, N. D.: Ber. **46,** 160 (1913); J. Russ. Phys. Chem. Soc. **44,** 1870, 1873 (1912).

(158) Ind. Eng. Chem. **34,** 68 (1942): "Plasticizers manufactured in America and commercially available."

(159) Trade advertisements.

THE CHEMISTRY OF THE ORGANIC ISOCYANATES

J. H. SAUNDERS AND R. J. SLOCOMBE

Monsanto Chemical Company, Phosphate Division, Anniston, Alabama

Received January 17, 1948

CONTENTS

I. Introduction ... 203
II. Methods of preparation ... 203
  A. Phosgene reactions ... 203
  B. Curtius, Hofmann, Lossen rearrangements ... 205
  C. Double decomposition reactions ... 206
  D. Miscellaneous preparations ... 206
III. Reactions of isocyanates ... 207
  A. Active hydrogen compounds ... 207
  B. Polymerization ... 211
  C. Other reactions ... 213
IV. Uses of isocyanates ... 215
V. References ... 216

I. INTRODUCTION

During the period 1885–1900 a considerable store of information regarding the fundamental properties of isocyanates was discovered. However, it was not until some forty years later that the practical uses of these compounds were realized. Within the last eight years the industrial applications of isocyanates have progressed from almost zero to the point at which a study of such compounds is of major interest, particularly in the field of polymers. Evidence for this growth is found in the patent literature of recent years and in the reports of German industry.

Recently a brief review of the methods of preparation of the isocyanates and of their reactions with active hydrogen compounds has appeared (76), together with a more comprehensive discussion of the industrial uses of these compounds (77). This article has been written so that an exhaustive study of the preparations and reactions of the isocyanates may be readily available. In addition, a few illustrative applications of these compounds have been given.

II. METHODS OF PREPARATION

A great number of methods of preparation of isocyanates are reported in the literature. These can conveniently be classed according to the reaction involved. The most common method involves the reaction between an amine or its salt and phosgene. Curtius, Hofmann, or Lossen rearrangements and double decomposition reactions have also been widely used. In addition, a variety of miscellaneous methods will be mentioned.

A. Phosgene reactions

Hentschel, in 1884, showed that an isocyanate could be obtained from the reaction between phosgene and the salt of a primary amine (46). This reaction was modified by Gattermann and Schmidt, who claimed an almost quantitative yield of methyl isocyanate by their procedure (39). They treated molten methylamine hydrochloride with phosgene at 250°C. and obtained methylcarbamyl chloride, which was decomposed by heating with lime.

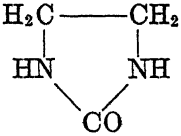
$$CH_3NH_2 \cdot HCl + COCl_2 \rightarrow CH_3NHCOCl + 2HCl$$
$$2CH_3NHCOCl + 2CaO \rightarrow 2CH_3NCO + CaCl_2 + Ca(OH)_2$$

In later years several modifications of this reaction have been developed. High-boiling isocyanates can be prepared more readily by a reaction between a slurry of the amine hydrochloride in a suitable solvent and phosgene. Solvents such as ethyl acetate (90), toluene (103), and *o*-dichlorobenzene (24) have been used to advantage. Yields are usually good. For example, *p*-nitrophenyl isocyanate has been prepared in 85–95 per cent yield by this method (90). The use of the carbamate salt was found to be superior to the use of the hydrochloride for the preparation of hexamethylene diisocyanate (24), probably because it is more soluble in the medium used than is the hydrochloride.

$$H_2N(CH_2)_6NH_2 + CO_2 \rightarrow H_3\overset{+}{N}(CH_2)_6NHCOO^- \xrightarrow{2COCl_2}$$
$$OCN(CH_2)_6NCO + 4HCl + CO_2$$

The lower-molecular-weight diisocyanates, such as ethylene and tetramethylene diisocyanate, have not been made successfully by this method, because of intramolecular urea formation.

$$H_3\overset{+}{N}CH_2CH_2NHCOO^- + COCl_2 \rightarrow$$



A more complete discussion of the liquid-phase phosgenation reactions has been given by Pinner (76).

A gas-phase reaction between an amine and phosgene at 180–400°C., in the presence of a catalyst such as bleached clay impregnated with barium chloride, zinc chloride, or sodium bisulfate, was used in Germany (69). Yields as high as 80 per cent were claimed for isocyanates containing as many as seven carbon atoms per molecule. The method was not found to be satisfactory for isocyanates of very high boiling points or for diisocyanates.

At about the same time a similar reaction procedure was developed in this country, with somewhat more promising results. Slocombe and Hardy (92) found that isocyanates could be prepared very rapidly and in good yields, using a vapor-phase process. No catalyst was necessary. The amine vapor and phosgene were mixed efficiently at about 275°C. and the products cooled. The carbamyl chloride corresponding to the amine used was isolated. The higher-boiling isocyanates were obtained by refluxing the carbamyl chloride in benzene or toluene solution. The low-boiling isocyanates were obtained by treating the carbamyl chloride with a tertiary amine. Yields were consistently high for the isocyanates of nine or fewer carbon atoms per molecule, usually 75–86 per cent.

It has been shown that the isocyanate itself was the product of the reaction at 275°C. (85). However, the carbamyl chloride was isolated because the isocyanate, when passed through a cold condenser, combined with an equivalent amount of hydrogen chloride.

$$\mathrm{RNH_2 + COCl_2 \xrightarrow{275°C.} RNCO + 2HCl}$$

$$\mathrm{RNCO + HCl \xrightarrow{25°C.} RNHCOCl}$$

When condensation was effected at 115°C., as was done for phenyl isocyanate, no carbamyl chloride was formed. In addition, methyl isocyanate was obtained directly by causing the hydrogen chloride to react preferentially with pyridine at 115°C.

The only side reaction of any significance in the phosgene processes is the formation of the corresponding disubstituted urea by the reaction of isocyanate with free amine.

$$\mathrm{RNCO + RNH_2 \rightarrow RNHCONHR}$$

This is almost eliminated by the use of the amine salt rather than free amine in the liquid-phase reactions, or by efficient mixing and a slight excess of phosgene in the vapor-phase process.

Urea formation is not always detrimental, however. A process used in Germany for the preparation of phenyl isocyanate consisted in the treatment of *sym*-diphenylurea with phosgene at 150°C., in a high-boiling solvent such as chlorinated naphthalene (59). Yields of 70–80 per cent were claimed.

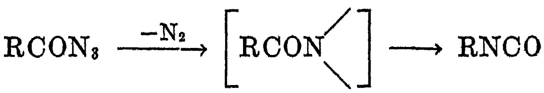
$$\mathrm{C_6H_5NHCONHC_6H_5 + COCl_2 \xrightarrow{150°C.} 2C_6H_5NCO + 2HCl}$$

The preparation of acyl isocyanates from amides and phosgene has also been reported (104).

$$\mathrm{RCONH_2 + COCl_2 \rightarrow RCONHCOCl}$$
$$\mathrm{RCONHCOCl + CaO \rightarrow RCONCO}$$

B. Curtius, Hofmann, Lossen rearrangements

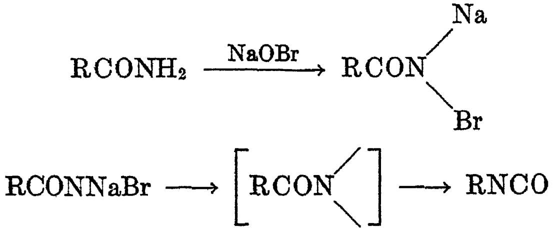
The method other than the phosgene reaction which has been used most is the Curtius rearrangement of an acid azide in a neutral solvent.



$$\mathrm{RCON_3 \xrightarrow{-N_2} \left[RCON\right] \longrightarrow RNCO}$$

The method was first developed to a considerable extent by Schroeter (88), who prepared several isocyanates by treating an acid chloride with sodium azide and warming the resulting product in benzene solution. Curtius (19, 21) has used the method for the preparation of substituted ethylene diisocyanates. However, he prepared the diazide by treating substituted succinic hydrazides with nitrous acid. Yields from the reaction are usually good, as in the case of undecyl isocyanate, which was obtained in 81–86 per cent yield (2). A complete survey of such preparations reported in the literature is given by Smith (96).

The Hofmann rearrangement of amides is useful only for those isocyanates which do not react readily with water, since an aqueous medium is required.



$$RCONH_2 \xrightarrow{NaOBr} RCON(Na)(Br)$$

$$RCONNaBr \longrightarrow [RCON] \longrightarrow RNCO$$

Pyman (78) has given a discussion of the limitations and scope of this reaction, as well as numerous examples. More recent results are given in the papers of Montagne and Guilmart (70) and of Cagniant and Bũu-Hoï (15).

The Lossen rearrangement of hydroxamic acids has not been used frequently.

$$RCONHOH \rightarrow RNCO + H_2O$$

The chemistry of the hydroxamic acids and the nature of the Lossen rearrangement have been reviewed recently by Yale (110). In addition, the preparation of aliphatic diisocyanates by this method is described in recent patents (18, 26).

C. Double decomposition reactions

The reaction between organic halides or sulfates and salts of cyanic acid was one of the first methods used for the preparation of isocyanates. Wurtz (108), in 1849, prepared alkyl isocyanates by this method.

$$R_2SO_4 + KCNO \rightarrow RNCO$$

Slotta and Lorenz (93) expressed the opinion that the reaction between the alkyl sulfate and potassium cyanate was the best method for the synthesis of methyl or ethyl isocyanate. Yields as high as 95 per cent were reported. In addition, acyl isocyanates may be prepared in this way, using acid chlorides (48)

$$RCOCl + AgCNO \rightarrow RCONCO$$

D. Miscellaneous preparations

A great variety of other methods has been used for the synthesis of isocyanates. In general, however, they were used only rarely, and are less practical than the reactions described above. The more important of them are given below.

N-Substituted carbamates may be decomposed to give the isocyanate from which the carbamate was derived. This is usually done by heating the carbamate at temperatures ranging from 135°C. to 500°C. (89), or by distilling the carbamate from phosphorus pentoxide (50, 105). Treatment with phosgene at 200°C. has also been described (73), but in the aromatic series this method seems to be specific for *N*-phenylcarbamates (17).

$$RNHCOOR' \xrightarrow{P_2O_5} RNCO$$

$$C_6H_5NHCOOR \xrightarrow{COCl_2} C_6H_5NCO$$

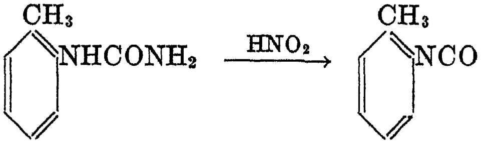
Diazonium chlorides, when treated with potassium cyanate in the presence of copper, are converted to isocyanates (38).

$$ArN_2Cl + KCNO \xrightarrow{Cu} ArNCO$$

Degner and von Pechmann (25) reported that the reaction between diazomethane and nitrourea produced methyl isocyanate.

$$H_2NCONHNO_2 + 3CH_2N_2 \rightarrow [HNCO + H_2NNO_2 + 3CH_2N_2] \rightarrow CH_3NCO + (CH_3)_2NNO_2$$

o-Tolylurea in the presence of nitrous acid is converted to the isocyanate (45).

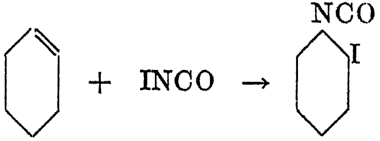


Either isocyanides (40) or isothiocyanates (61) may be oxidized with mercuric oxide to give the isocyanate.

$$RNC + HgO \rightarrow RNCO$$

$$RNCS + HgO \rightarrow RNCO$$

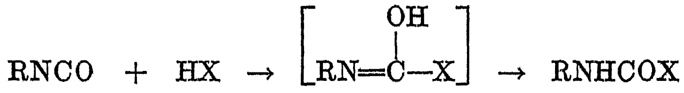
It has also been observed that olefins add iodoisocyanate almost quantitatively at −80°C. (7). The reaction may be used to characterize olefins, since crystalline ureas may easily be prepared.



III. REACTIONS OF ISOCYANATES

A. Active hydrogen compounds

The most characteristic reactions of isocyanates are those which involve compounds containing an active hydrogen.



$$RNCO + HX \rightarrow \left[RN{=}\overset{\overset{\displaystyle OH}{|}}{C}{-}X\right] \rightarrow RNHCOX$$

Generally the reaction proceeds readily at ordinary temperatures or, after moderate heating, without the use of catalysts. However, it is reported that a compound such as cobalt naphthenate and tertiary amines will accelerate the reaction (7, 82).

Isocyanates are hydrolyzed by water with varying degrees of rapidity. Some —for example, octadecyl isocyanate—can be emulsified and will be stable as such for as much as a day. Others are hydrolyzed more readily, with the formation of disubstituted ureas (107, 108).

$$RNCO + H_2O \rightarrow RNHCOOH \rightarrow RNH_2 + CO_2$$

$$RNH_2 + RNCO \rightarrow RNHCONHR$$

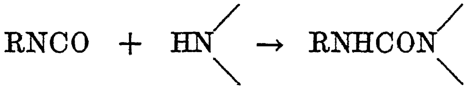
When alkali is used, however, urea formation is decreased considerably and the primary amine is the principal product (109). In general, isocyanates are extremely hygroscopic, and it is this affinity for water, together with subsequent urea formation, which makes handling and storage difficult. Extreme care must be used in drying all equipment used in handling the isocyanates.

Reaction with halogen acids leads to the formation of a carbamyl halide.

$$RNCO + HX \rightarrow RNHCOX$$

Such a reaction has been observed with hydrogen fluoride (13), hydrogen chloride (47, 63), and hydrogen bromide (37). The carbamyl halides are stable at room temperature, but tend to dissociate into isocyanate and hydrogen halide in the range of 90–100°C. (13, 63, 85).

Practically all compounds containing a hydrogen atom attached to a nitrogen atom will react with isocyanates.



$$RNCO + HN\langle \rightarrow RNHCON\langle$$

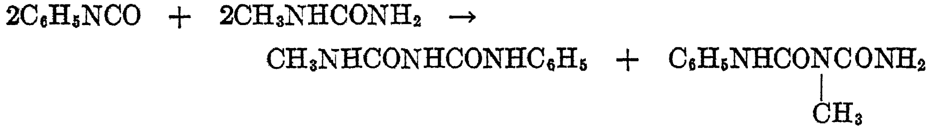
Amines react to give substituted ureas (87), amides give acyl ureas (14), while ureas give biurets (60, 62).

$$RNCO + R'_2NH \rightarrow RNHCONR'_2$$

$$RNCO + R'CONH_2 \rightarrow RNHCONHCOR'$$

$$RNCO + H_2NCONH_2 \rightarrow RNHCONHCONH_2$$

Biltz and Beck (5) have observed that reaction between phenyl isocyanate and methylurea gives two isomeric products.



$$2C_6H_5NCO + 2CH_3NHCONH_2 \rightarrow CH_3NHCONHCONHC_6H_5 + C_6H_5NHCON(CH_3)CONH_2$$

Hydroxylamine reacts with 2 moles of phenyl isocyanate (35).

$$2C_6H_5NCO + H_2NOH \rightarrow C_6H_5NHCONHOCONHC_6H_5$$

However, if the isocyanate is added dropwise to a large excess of cold hydroxylamine, the urea is formed (35).

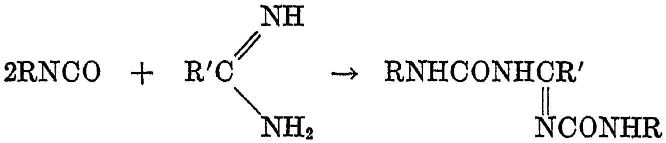
$$C_6H_5NCO + H_2NOH \rightarrow C_6H_5NHCONHOH$$

In contrast, however, benzohydroxamic acid is reported to give preferential cleavage of the O—H bond (66).

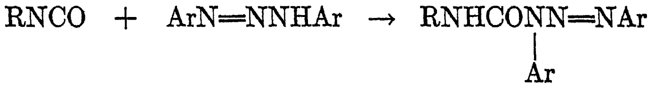
$$RNCO + C_6H_5CONHOH \rightarrow C_6H_5CONHOCONHR$$

Other nitrogen compounds, such as hydrazines (20), amidines (75), nitramines (87), and diazoamino (43) compounds, behave as expected.

$$\text{RNCO} + \text{H}_2\text{NNHR} \rightarrow \text{RNHCONHNHR}$$



$$\text{RNCO} + \text{R'NHNO}_2 \rightarrow \text{RNHCON(R')NO}_2$$



$$\text{RNCO} + \text{ArN{=}NNHAr} \rightarrow \text{RNHCON(Ar)N{=}NAr}$$

Besides the expected product, Caldwell and coworkers (16) have observed that treatment of the phenylhydrazone of acetone with 2 moles of phenyl isocyanate in benzene produces α,β-di(phenylcarbamyl)phenylhydrazine.

$$\begin{aligned}2(\text{CH}_3)_2\text{C{=}NNHC}_6\text{H}_5 + 3\text{C}_6\text{H}_5\text{NCO} \rightarrow\ & (\text{CH}_3)_2\text{C{=}NN(C}_6\text{H}_5\text{)CONHC}_6\text{H}_5 \\ & + \text{C}_6\text{H}_5\text{N(CONHC}_6\text{H}_5\text{)NHCONHC}_6\text{H}_5\end{aligned}$$

Reaction with a secondary amine affords a convenient method of analysis (34, 98). An isocyanate may be titrated stoichiometrically with di-*n*-butylamine with good accuracy and reproducibility.

Reaction with amino and amido groups of proteins may account for any toxic effects of the isocyanates. Reports from Germany concerning toxicity are contradictory. However, during the course of several years' experience with isocyanates in this laboratory, only one minor skin irritation of a temporary nature has been observed. When reasonable care in handling was observed, no difficulties were encountered. Some isocyanates are lachrymators, however. This property apparently varies with the vapor pressure of the isocyanate. For example, *m*-tolylene diisocyanate is not a bad lachrymator, while phenyl isocyanate is.

Similarly, compounds containing hydrogen atoms attached to oxygen react with isocyanates. All types of alcohols—primary, secondary, tertiary, and polyhydric—react to give carbamates (44, 56).

$$\text{RNCO} + \text{R'OH} \rightarrow \text{RNHCOOR'}$$

One exception is triphenylcarbinol, which gives no reaction (56). Phenols, including polyhydric phenols, react, especially in the presence of aluminum chloride (65).

It has been observed in this laboratory that tertiary alcohols may be dehydrated by heating with isocyanates (91).

$$2\text{C}_6\text{H}_5\text{NCO} + (\text{CH}_3)_3\text{COH} \rightarrow (\text{CH}_3)_2\text{C{=}CH}_2 + \text{C}_6\text{H}_5\text{NHCONHC}_6\text{H}_5$$

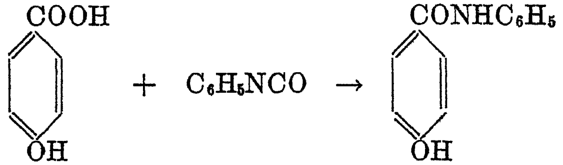
Acids, such as acetic acid, react to give mixed anhydrides, which readily decompose to amides (28, 71).

$$\begin{aligned}\mathrm{RNCO} + \mathrm{CH_3COOH} &\rightarrow \mathrm{RNHCOOCOCH_3} \\ &\rightarrow \mathrm{RNHCOCH_3} + \mathrm{CH_3COOCOCH_3} + \mathrm{CO_2} + \mathrm{(RNH)_2CO}\end{aligned}$$

The hydroxyl group of a hydroxy acid is sometimes more reactive than the carboxyl group, as illustrated by the reaction of β-hydroxyisobutyric acid (10).

$$\mathrm{RNCO} + \mathrm{HOCH_2CH(CH_3)COOH} \rightarrow \mathrm{RNHCOOCH_2CH(CH_3)COOH}$$

However, Humnicki (54) has reported that *o*-, *m*-, and *p*-hydroxybenzoic acids give the amide exclusively.

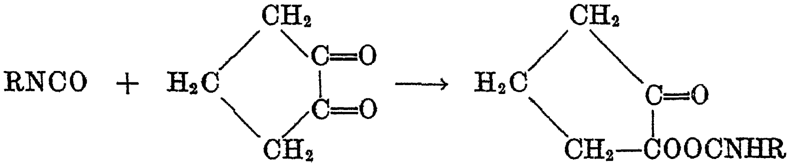


In general, sulfur compounds behave in the same manner as their oxygen analogues.

Compounds which are capable of enolizing are reactive toward isocyanates. For instance, nitromethane (67), malonic ester (29), acetoacetic ester (67), and similar compounds give the typical reaction in the presence of sodium.

$$\mathrm{RNCO} + \mathrm{NaCH(COOC_2H_5)_2} \rightarrow \mathrm{RNHCOCH(COOC_2H_5)_2}$$

O-Acylation occurs in the case of 1,2-cyclopentadione (27).



A few other reactions of isocyanates are known. A Friedel–Crafts reaction has been observed with aluminum chloride (64).

$$\mathrm{RNCO} + \mathrm{ArH} \xrightarrow{\mathrm{AlCl_3}} \mathrm{RNHCOAr}$$

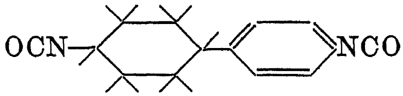
A consideration of the relative reactivity of active hydrogen compounds toward isocyanates indicates that amines react much faster than alcohols, which in turn react faster than water. An example of such a sequence is found in the reaction between ethanolamine and 1 mole of phenyl isocyanate, in which a urea is formed rather than a carbamate (57).

$$\mathrm{C_6H_5NCO} + \mathrm{H_2NCH_2CH_2OH} \rightarrow \mathrm{C_6H_5NHCONHCH_2CH_2OH}$$

Davis and Farnum (23) have studied the relative rates of reaction of phenyl isocyanate with several alcohols in benzene at 26°C. It was found that all primary alcohols investigated reacted at about the same rate. Secondary alcohols reacted about 0.3 as fast as the primary, while tertiary alcohols reacted about 0.005 as fast as the primary. Davis and Ebersole (22) extended the investigation to amines. In ether, at 0°C., primary aliphatic amines reacted about nine times as fast as ammonia, whereas aniline reacted only about one-half as fast as ammonia.

Apparently the basicity of the atom to which the active hydrogen is bound, as well as steric factors, influences greatly the rate of reaction with the isocyanates.

Some recent work in Germany has shown that the isocyanates themselves vary in reactivity. The rate of reaction of aromatic isocyanates with alcohols is decreased greatly by the presence of bulky groups in the ortho position. It was also found that secondary aliphatic and alicyclic isocyanates are much less reactive toward alcohols than are aromatic or benzyl isocyanates. Primary aliphatics fall in between these two classes. This difference has been used to advantage in such compounds as 4,4′-diisocyanatohexahydrobiphenyl.

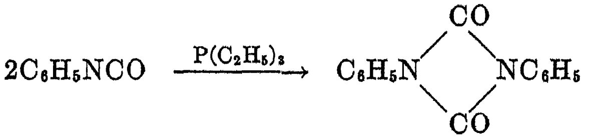


In this compound the isocyanate group attached to the aromatic nucleus is much more reactive than the other. This difference can be used to advantage, since under mild conditions the isocyanate group on the aromatic ring is reactive. After this initial reaction is completed the isocyanate group on the cyclohexyl ring is still available for reactions under more drastic conditions (6).

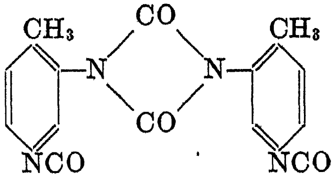
Many of the normal reactions of isocyanates with active hydrogen compounds may be reversed by heating. For example, carbamates may be decomposed to give the isocyanate and alcohol, as described in the section on methods of preparation (6, 17, 50, 73, 80, 89, 105). Carbamyl chlorides and fluorides, as well as certain ureas, may be decomposed similarly (6).

B. Polymerization

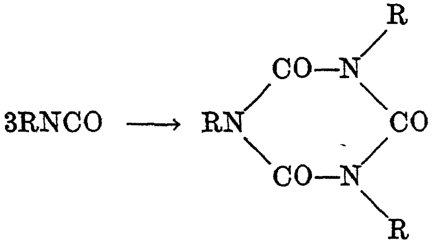
A second general type of reaction of the isocyanates is polymerization. Several catalysts have been used to bring about varying degrees of polymerization. In the presence of triethylphosphine most aromatic isocyanates dimerize, presumably to a compound of the structure shown (8, 36, 51, 52).



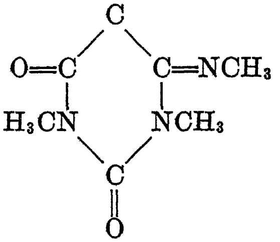
Heating phenyl isocyanate with pyridine also results in dimer formation (79, 97). It has been reported that 2,4-tolylene diisocyanate slowly formed a dimer on standing (6).



Ethyl isocyanate, on the other hand, gives a trimer when brought into contact with triethylphosphine (51). Other catalysts which have been used to induce the trimerization of either aromatic or aliphatic isocyanates are calcium acetate (36), potassium acetate (53), sodium formate (53), sodium carbonate (53), sodium methoxide (67), triethylamine (49), and oxalic acid (3). Peroxides and Friedel–Crafts catalysts are also effective in bringing about polymerization (6). The generally accepted structure for the trimer is that of a trisubstituted cyanuric acid.

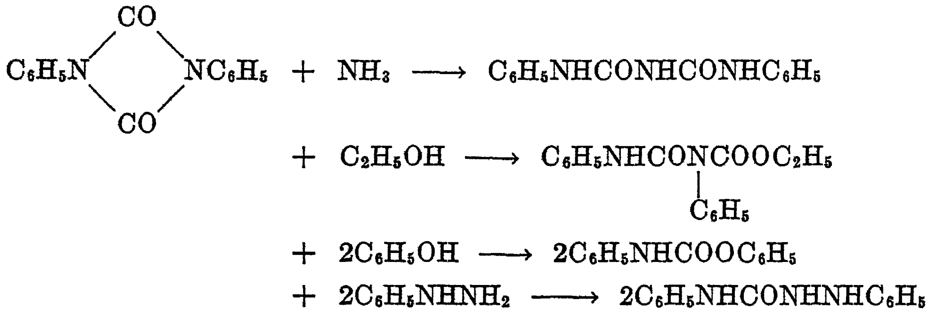


Slotta and Tschesche (94) have reported that a different type of trimer is formed from methyl isocyanate when triethylphosphine is the catalyst. They assigned it the structure of 3,5-dimethyl-2-methylimino-4,6-diketo-1,3,5-trioxdiazine.



Little or no definite information is available on high-molecular-weight polymers of the isocyanates.

The aromatic isocyanates can be regenerated from their dimers by heating (101), although heating to a higher temperature (250°C.) reportedly gives the trimer (101). Phenyl isocyanate dimer reacts with ammonia to give ω-diphenylbiuret (52), with alcohol to give ethyl *N*,*N'*-diphenylallophanate (36), with phenol to give phenyl carbanilate (52), and with phenylhydrazine to give 1,4-diphenylsemicarbazide (30).



C. Other reactions

Known reactions of isocyanates not involving active hydrogens or polymerization are few. Slotta and Tschesche (95) reported that methyl isocyanate did not condense with carbon oxysulfide, carbon disulfide, phenyl isothiocyanate, acetonitrile, nitromethane, quinone, acetylene, ethylene, or amylene under the influence of triethylphosphine. With aldehydes, aldoketenes, carbon suboxide, and cyanic acid in the presence of triethylphosphine, only polymers of these substances and the trimer of methyl isocyanate were obtained. No condensation occurred with either dimethylketene or diphenylketene. Treatment with diazomethane gave an insoluble, amorphous substance which could not be identified.

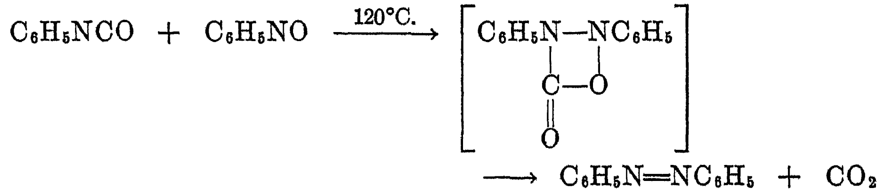
Staudinger (100) has found that dimethylketene will react with phenyl, α-naphthyl, and *p*-nitrophenyl isocyanates to give amorphous substances of molecular weight 3000–6000. He has confirmed that dimethylketene does not react with methyl isocyanate; *p*-anisyl isocyanate is also unreactive. Trimethylamine served as a catalyst in all of his experiments.

Staudinger (99) has attempted to compare isocyanates with ketenes in certain of their reactions.

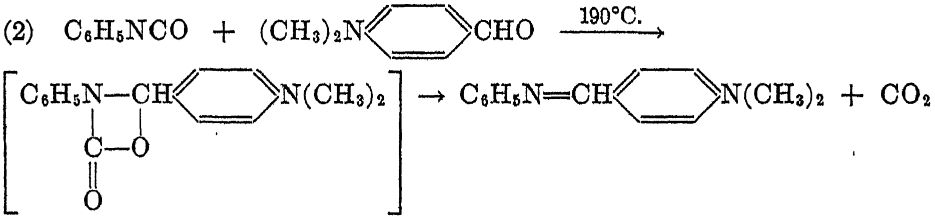
$$\mathrm{R{-}CH{=}C{=}O} \qquad \mathrm{R{-}N{=}C{=}O}$$

Unlike ketenes, however, isocyanates do not form four-membered rings at low temperatures with reactive unsaturated compounds, such as nitrosobenzene. However, at higher temperatures compounds are formed which he considers to be degradation products of the additive compounds.

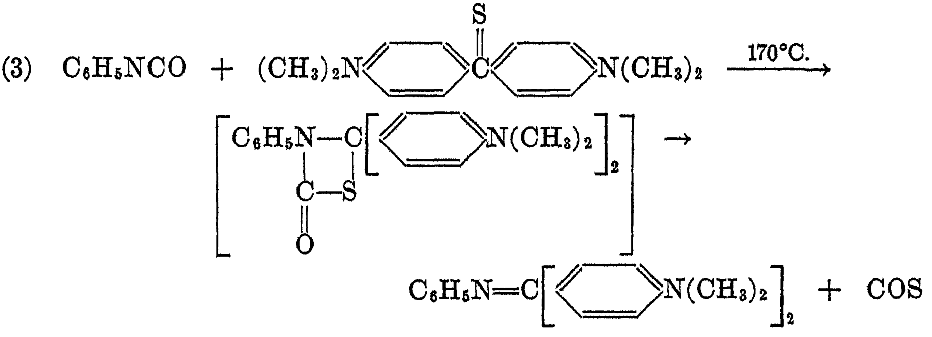
(1)



(2)



(3)



Reactions of isocyanates with active hydrogen compounds are analogous to the corresponding reactions of ketenes.

The isocyanates vary in their reactions when heated. Phenyl isocyanate, on long heating under pressure, gives carbodiphenylimide (101).

$$2C_6H_5NCO \xrightarrow{\text{heat}} C_6H_5N{=}C{=}NC_6H_5 + CO_2$$

tert-Butyl isocyanate, when heated to 180°C., gives isobutylene and cyanuric acid (11). However, the most common reaction is polymerization.

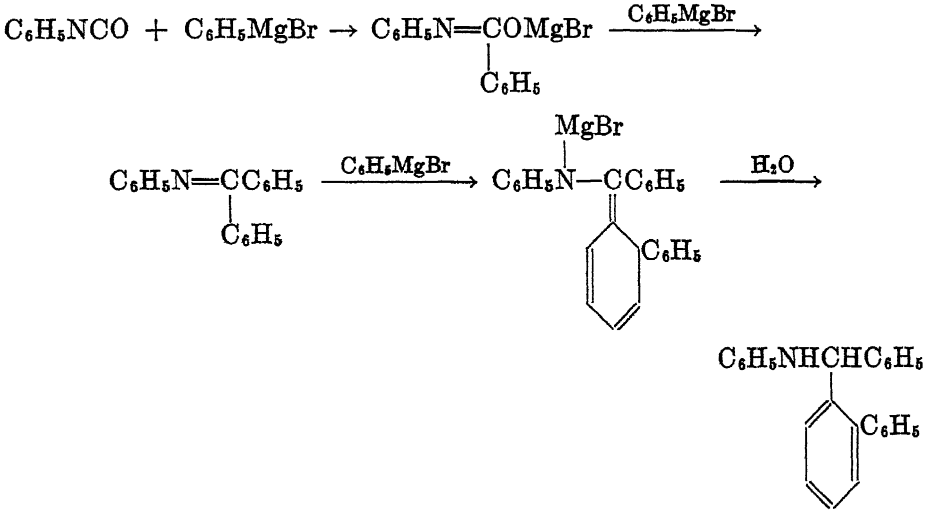
Another general reaction of isocyanates is amide formation upon treatment with a Grignard reagent (9).

$$RNCO + R'MgX \xrightarrow{H_2O} RNHCOR'$$

Entemann and Johnson (31) have shown that the reactivity of the isocyanate group toward a Grignard reagent is less than that of the acetyl group, but greater than that of the fluoroformyl group.

$$CH_3CO{-} > {-}NCO > {-}COF$$

In contrast to the expected amide, however, Gilman (42) obtained a 45 per cent yield of *o*-phenylbenzohydrylaniline from the reaction between phenyl isocyanate and an excess of phenylmagnesium bromide. The proposed reaction sequence was that shown below.

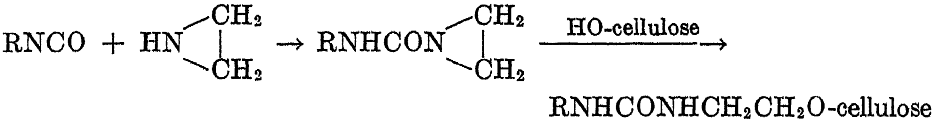


The remaining known reactions of isocyanates are few. Phenyl isocyanate on treatment with chlorine or bromine gives a dichloride or dibromide (44), while phosphorus pentachloride converts it to a chloride which can be reduced with zinc dust to methylaniline (44). Phosphorus pentasulfide converts phenyl isocyanate to phenyl isothiocyanate (68). Reduction with hydrogen and nickel at 190°C. produces methylaniline, carbanilide, aniline, methane, and carbon dioxide (83).

IV. USES OF ISOCYANATES

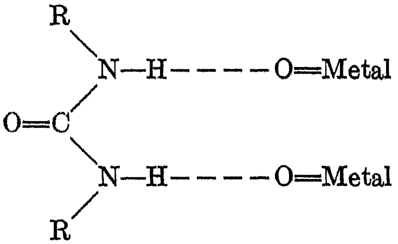
The principal industrial uses of isocyanates have been in the field of polymers. Copolymers have been prepared from diisocyanates and bifunctional compounds such as glycols (55, 58, 81, 86, 103), diamines (12), and dicarboxylic acid amides (4). Such polymers, especially the polyurethans, have been reported to be harder than nylon, to absorb water less readily, to be unreactive (58). Terpolymers have been made from isocyanates, ethylenimine, and carbon disulfide (32).

Modification of polymers by isocyanate treatment has been the object of much interest. One important example is the foaming of alkyd resins by isocyanates. Such resins, which contain an excess of carboxyl groups, react with diisocyanates at low temperatures with the evolution of carbon dioxide. The gas which is formed causes the plastic to foam and fill the enclosing container and to adhere to the walls of the container (55). Treatment of cellulose with the urea formed from octadecyl isocyanate and ethylenimine renders the cellulose water-repellent. It has been proposed that the reaction proceeds in this manner (72, 73).



$$\mathrm{RNCO} + \mathrm{HN}\begin{matrix}\diagup \mathrm{CH_2} \\ | \\ \diagdown \mathrm{CH_2}\end{matrix} \rightarrow \mathrm{RNHCON}\begin{matrix}\diagup \mathrm{CH_2} \\ | \\ \diagdown \mathrm{CH_2}\end{matrix} \xrightarrow{\text{HO-cellulose}} \mathrm{RNHCONHCH_2CH_2O\text{-}cellulose}$$

Another very important use of isocyanates is in the manufacture of adhesives for bonding rubber to foreign objects, such as rayon or metal. The Germans were very successful in the use of a triisocyanate, tri(*p*-isocyanatophenyl)methane, in such adhesives. Bayer has suggested that the rubber-to-metal adhesion may be due to the presence of a film of moisture and oxide on the metal surface. The water would produce ureide bridges between two isocyanate groups, and such bridges could then form complexes with the metal oxide films. This would account for adhesion to the metal interface. Adhesion to the rubber interface was thought to be due to solubility of the isocyanate in rubber and to secondary valence forces (6).



Many other industrial uses of isocyanates, such as varnish treatment, tanning of leather, paper treatment, and production of electrical insulators, are named in the patent literature.

Outside the field of polymers the uses of isocyanates are few, but show promise of growing rapidly. For example, isopropyl *N*-phenylcarbamate, which appears to be a specific killer of weedy grasses (1), is receiving much attention. Antiallergic substances have been made from isocyanates and proteins containing histamine (33). Carbamates are also of interest in cancer study.

A fairly comprehensive review of the industrial uses of isocyanates has been given recently by Pinner (77).

One other significant use for specific isocyanates is the identification of organic compounds. β-Naphthyl isocyanate is a good reagent for the preparation of crystalline derivatives of most phenols (84), while *p*-nitrophenyl isocyanate is a good reagent for alcohols and amines (102). *p*-Triphenylmethylphenyl and 2-fluorenyl isocyanates have also been recommended for alcohols (106). In addition, Grignard reagents, and consequently alkyl and aryl halides, can conveniently be identified by treatment with 2-naphthyl isocyanate to give the corresponding amide (41).

The authors wish to express their appreciation to Dr. Edgar E. Hardy for his constant and stimulating interest in the preparation of this paper.

V. REFERENCES

(1) Allard, Ennis, De Rose, and Weaver: Botan. Gaz. **107**, 589 (1946).
(2) Allen and Bell: Org. Syntheses **24**, 94 (1944).
(3) Bailey and McPherson: J. Am. Chem. Soc. **39**, 1338 (1917).
(4) Belgian patent 448,187.
(5) Biltz and Beck: Ber. **58B**, 2187 (1925).
(6) B.I.O.S. Final Report No. 719, Interview with Professor Otto Bayer.
(7) Birckenbach and Linhard: Ber. **64B**, 961, 1076 (1931).
(8) Blair and Smith: J. Am. Chem. Soc. **56**, 907 (1934).
(9) Blaise: Compt. rend. **132**, 40 (1901).
(10) Blaise and Hermann: Ann. chim. [8] **17**, 393 (1909).
(11) Braumer: Ber. **12**, 1874 (1879).
(12) British patent 535,139.
(13) Buckley, Piggott, and Welch: J. Chem. Soc. **1945**, 864.
(14) Busch, Blume, and Pungs: J. prakt. Chem. [2] **79**, 513 (1909).
(15) Cagniant and Buu-Hoï: Bull. soc. chim. **10**, 349 (1943).
(16) Caldwell, Chapman, Goodwin, and Wilson: J. Chem. Soc. **1932**, 2036.
(17) Chabrier: Compt. rend. **214**, 362 (1942).
(18) Cupery: U. S. patent 2,346,665.
(19) Curtius, v. Bruning, and Derlon: J. prakt. Chem. **125**, 63 (1930).
(20) Curtius and Burkhardt: J. prakt. Chem. [2] **58**, 205 (1898).
(21) Curtius and Hectenberg: J. prakt. Chem. **105**, 289 (1923).
(22) Davis and Ebersole: J. Am. Chem. Soc. **56**, 885 (1934).
(23) Davis and Farnum: J. Am. Chem. Soc. **56**, 883 (1934).
(24) DeBell, Goggin, and Gloor: *German Plastics Practice*, p. 300. Murray Printing Company, Cambridge, Massachusetts (1946).
(25) Degner and v. Pechmann: Ber. **30**, 646 (1897).
(26) Dickey, Straley, and Stanin: U. S. patent 2,394,597.
(27) Dieckmann: Ber. **35**, 3210 (1902).
(28) Dieckmann and Breest: Ber. **39**, 3052 (1906).
(29) Dieckmann, Hoppe, and Stein: Ber. **37**, 4627 (1904).
(30) Dieckmann and Kammerer: Ber. **38**, 2985 (1905).
(31) Entemann and Johnson: J. Am. Chem. Soc. **55**, 2900 (1933).
(32) Esselmann and Dusing: German patent 738,667.
(33) Fell: U. S. patents 2,372,066; 2,376,424.
(34) F.I.A.T. Final Report No. 712, January 21, 1946.
(35) Fischer: Ber. **22**, 1930 (1889).

(36) Frentzel: Ber. **21,** 411 (1888).
(37) Gal: Bull. soc. chim. [2] **6,** 437 (1866).
(38) Gattermann and Cantzler: Ber. **23,** 1224 (1890); **25,** 1086 (1892).
(39) Gattermann and Schmidt: Ann. **244,** 29 (1888).
(40) Gautier: Ann. **149,** 313 (1869).
(41) Gilman and Furry: J. Am. Chem. Soc. **50,** 1214 (1928).
(42) Gilman, Kirby, and Kinney: J. Am. Chem. Soc. **51,** 2252 (1929).
(43) Goldschmidt and Molinari: Ber. **21,** 2559 (1888).
(44) Gumpert: J. prakt. Chem. [2] **31,** 119 (1885); [2] **32,** 278 (1885).
(45) Haager and Doht: Monatsh. **27,** 271 (1906).
(46) Hentschel: Ber. **17,** 1284 (1884).
(47) Hentschel: Ber. **18,** 1178 (1885).
(48) Hill and Degnan: U. S. patent 2,379,486.
(49) Hofmann: Jahrb. Fortschritte Chem. **1862,** 335.
(50) Hofmann: Ber. **3,** 653 (1870).
(51) Hofmann: Ber. **3,** 765 (1870).
(52) Hofmann: Ber. **4,** 246 (1871).
(53) Hofmann: Ber. **18,** 765 (1885).
(54) Humnicki: Roczniki Chem. **11,** 674 (1931); Chem. Abstracts **26,** 5556 (1932).
(55) Kline: Modern Plastics **23,** 152-A (1945).
(56) Knoevenagel and Schurenberg: Ann. **297,** 148 (1897).
(57) Knorr and Rossler: Ber. **36,** 1280 (1903).
(58) Krausen: Silk J. & Rayon World **21,** 28, 36 (1946).
(59) Krey: *Production of Phenyl Isocyanate,* O.P.B. Report No. 58913, Frame No. 1082–1087.
(60) Kuhn and Hentschel: Ber. **21,** 504 (1888).
(61) Kuhn and Liebert: Ber. **23,** 1536 (1890).
(62) Lakra and Dains: J. Am. Chem. Soc. **51,** 2220 (1929).
(63) Lengfeld and Stieglitz: Am. Chem. J. **16,** 71 (1894).
(64) Leuckart: Ber. **18,** 873 (1885).
(65) Leuckart and Schmidt: Ber. **18,** 2339 (1885).
(66) Marquis: Compt. rend. **143,** 1165 (1906).
(67) Michael: Ber. **38,** 22 (1905).
(68) Michael and Palmer: Am. Chem. J. **6,** 258 (1884).
(69) Modersohn: *Action of Phosgene on Primary and Secondary Amines in the Gas Phase,* O.P.B. Report No. 707.
(70) Montagne and Guilmart: Bull. soc. chim. **12,** 836 (1945).
(71) Naegali and Tyabji: Helv. Chim. Acta **17,** 931 (1934); **18,** 142 (1935).
(72) O.P.B. Report 1576, p. 10.
(73) Piggott and Statham: British patent 485,761.
(74) Pingree and Dahlen: *Textile Finishing Treatments,* Vol. I. Hobart Publishing Company, Washington, D. C.
(75) Pinner: Ber. **23,** 2923 (1890).
(76) Pinner: Plastics (London) **11,** 206 (1947).
(77) Pinner: Plastics (London) **11,** 257 (1947).
(78) Pyman: J. Chem. Soc. **103,** 852 (1913).
(79) Raiford and Freyermuth: J. Org. Chem. **8,** 230 (1943).
(80) Raiford and Shelton: J. Org. Chem. **4,** 207 (1939).
(81) Rinke and Weikart: German patent 728,002.
(82) Rothrock: U. S. patent 2,374,136.
(83) Sabatier and Mailche: Compt. rend. **144,** 825 (1907); Ann. chim. [8] **16,** 99 (1909).
(84) Sah: Rec. trav. chim. **58,** 453 (1939).
(85) Saunders, Slocombe, and Hardy: Forthcoming publication.
(86) Schlack: U. S. patent 2,343,808.

(87) SCHOLL AND HOLDERMANN: Ann. **345**, 376 (1907).

(88) SCHROETER: Ber. **42**, 2336, 3356 (1909).

(89) SCHWEITZER: U. S. patent 2,409,712

(90) SHRINER, HORNE, AND COX: *Organic Syntheses*, Collective Volume II, p. **453**. John Wiley and Sons, Inc., New York (1943).

(91) SLOCOMBE: Unpublished results.

(92) SLOCOMBE AND HARDY: Forthcoming publication.

(93) SLOTTA AND LORENZ: Ber. **58B**, 1320 (1925).

(94) SLOTTA AND TSCHESCHE: Ber. **60B**, 295 (1927).

(95) SLOTTA AND TSCHESCHE: Ber. **60B**, 1021 (1927).

(96) SMITH: *Organic Reactions*, Vol. III, p. 337. John Wiley and Sons, Inc., New York (1946).

(97) SNAPE: J. Chem. Soc. **49**, 254 (1886).

(98) STAGG: Analyst **71**, 557 (1946).

(99) STAUDINGER AND ENDLE: Ber. **50**, 1042 (1917).

(100) STAUDINGER, FELIX, AND GEIGER: Helv. Chim. Acta **8**, 314 (1925).

(101) STOLLE: Ber. **41**, 1125 (1908).

(102) VAN HOOGSTRATEN: Rec. trav. chim. **51**, 414 (1932).

(103) VITTENET: Bull. soc. chim. [3] **21**, 957 (1899).

(104) WALTMANN AND WOLF: U. S. patent 2,346,202; Canadian patent 420,235.

(105) WENKER: J. Am. Chem. Soc. **58**, 2608 (1936).

(106) WITTEN AND REID: J. Am. Chem. Soc. **69**, 2470 (1947).

(107) WURTZ: Compt. rend. **27**, 242 (1848).

(108) WURTZ: Ann. **71**, 326 (1849).

(109) WURTZ: Compt. rend. **28**, 224 (1849).

110) YALE: Chem. Revs. **33**, 209 (1943).

THE NATURE OF THE GLASSY STATE AND THE BEHAVIOR OF LIQUIDS AT LOW TEMPERATURES

WALTER KAUZMANN

Department of Chemistry, Princeton University, Princeton, New Jersey

Received March 1, 1948

CONTENTS

I. Introductory summary 220
  A. The concept of metastability 220
  B. The nature of the metastability of supercooled liquids 221
II. The glass transformation 224
  A. The characteristics of the glass transformation 224
  B. Equilibrium and dynamic mechanisms in the glass transformation 227
  C. The identification of the molecular motions involved in the glass relaxation process 230
  D. The identification of the degrees of freedom involved in the glass transformation 233
  E. Interpretation according to the hole theory of liquids 234
  F. The effect of vitrification on properties other than the thermal expansion and the specific heat 236
  G. The kinetics of vitrification 238
  H. The usefulness of glasses in theoretical investigations of the liquid state 239
  I. The concept of torpid states of matter 240
III. The behavior of the non-vitreous liquid at low temperatures 242
  A. The experimental evidence 243
  B. An apparent paradox 244
  C. A resolution of the paradox 245
  D. Comparison of the rates of entropy loss in hydrogen-bonded and non-hydrogen-bonded liquids 248
  E. Interpretation in terms of a simple liquid model 249
IV. Appendix A 252
V. Appendix B 253
VI. References 253

When the temperature of a supercooled liquid is brought below approximately two-thirds of the normal freezing point, a rather sudden drop in the specific heat and the thermal expansion coefficient is observed. It is widely agreed that this "glass transformation" is caused by a relaxation effect, through which some process in the amorphous material occurs too slowly at low temperatures to permit thermodynamic equilibrium to be established in all degrees of freedom. It is shown that the molecular movements involved in the relaxation process must resemble closely the movements in viscous flow and dielectric relaxation. Movements of this type permit the liquid structure to change following temperature and pressure changes. Thus it is the contribution of changing liquid structure to the thermodynamic properties which is absent at low temperatures and results in the drop in specific heat and coefficient of expansion.

Accordingly vitrification can always be avoided in principle by making measurements sufficiently slowly. With a view to understanding the "true" thermodynamics of supercooled liquids as observed in such slow experiments the trends in the observed thermodynamic properties of liquids above the glass-transformation

temperature are examined. These trends seem to indicate that the entropies and enthalpies, but not the free energies, of many non-vitreous liquids would become less than those of the corresponding crystalline phases at temperatures well above the absolute zero. This paradoxical result would seem to imply that there is a temperature below which a non-vitreous liquid cannot exist, owing to spontaneous crystallization. There are good theoretical reasons for believing in the existence of such a "pseudocritical temperature."

I. INTRODUCTORY SUMMARY

A. *The concept of metastability*

As is well known, some liquids can be held at temperatures well below their freezing points over very long periods without crystallizing. Liquids in such a state are said to be *supercooled.*

In order to describe this behavior, Ostwald (62) introduced the concept of the *metastable state.* A mechanical system was said to be in a metastable condition if all small displacements of the particles of which it was composed resulted in an increase in the potential energy of the system, while certain large displacements could bring about a decrease in the potential energy. The classic example of this, cited by him, was a marble in a bowl held at some distance above a table. By analogy (and with slight modification of Ostwald's language) we may say that a thermodynamic system at a specified temperature is in a metastable condition or state if all small isothermal changes of its independent thermodynamic variables result in an increase in its free energy, while certain large isothermal changes in these variables can bring about a state with lower free energy. In this sense, then, the supercooled liquid is believed to be in a metastable state with respect to its crystalline phase.

The idea of metastability, by definition, requires that there be states of higher free energy than the metastable state along all possible routes between the metastable and stable states of a thermodynamic system. These intermediate states may be said to give rise to *free energy barriers* impeding the transformation of the metastable into the stable state. A supercooled liquid, in crystallizing, must go through intermediate states having higher free energies than either the liquid or the crystal. Spontaneous crystallization is then interpreted as the result of random accumulations (by thermal fluctuations) of sufficient free energy for the liquid to pass over these barriers.

Conversely, we may say that whenever a free energy barrier exists between two states of a system, we should expect, at least in principle, to be able to distinguish metastable states of that system. The feasibility of studying such metastable states experimentally depends, however, upon two factors: (*a*) the possibility of bringing the system into the metastable state in question, and (*b*) the possibility of keeping the system in that metastable state long enough to make the necessary observations. With supercooled liquids the first factor never presents any difficulty but the second frequently does: most liquids crystallize spontaneously below their freezing points long before we have a chance to measure any of their properties. On the other hand, numerous metastable states of condensed phases and other systems are conceivable (e.g., a hexagonal close-packed sodium chloride crystal, or a wurtzite form of carbon) but cannot be studied experimentally because we do not know how to prepare them, even though it seems likely that, once prepared, they would probably not readily revert back to the more stable forms. The problem of manufacturing diamonds is, of course, entirely of this nature, as are most of the problems of synthetic inorganic and organic chemistry.

Eyring has shown that many physical processes in condensed phases involve passages over free energy barriers. Among these processes are plastic flow, molecular diffusion, and dielectric relaxation. According to the arguments presented above, therefore, we must expect metastable states to occur supported by the free energy barriers involved in these processes. We shall see in this paper that the glassy or vitreous state of liquids is such a metastable state.

B. The nature of the metastability of supercooled liquids

The work of Tammann and others (23, 92, 102) has shown that the crystallization process occurs in two steps: first crystal nuclei must form, and then these nuclei must grow. Depending on the temperature and the substance, either of these two steps may determine the rate of spontaneous crystallization. Therefore, at least two types of free energy barrier may be involved in the metastability of the supercooled liquid. These two types of barrier are believed to be determined as follows: (*1*) The free energy barrier to crystal nucleus formation arises essentially because the melting point of small crystals is lower than that of large ones (see Appendix A). Thus, in any supercooled liquid, crystals smaller than a certain size are unstable, so that in order to form a stable nucleus one must first form crystallites having higher free energies than the same amount of liquid. (*2*) The free energy barrier to crystal growth, on the other hand, is simply that which prevents the movement of a molecule at a crystal–liquid interface from a liquid-like position to a crystal-like position. For temperatures sufficiently below the freezing point, Richards (75) has shown that the molecular movement in crystal growth is essentially a molecular rotation very closely similar to that involved in the orientation of dipoles in an electric field, so that the free energy barrier to crystal growth must be similar to that which gives rise to dielectric relaxation in dipolar liquids.

The practical limitations of the concept of a supercooled liquid as a metastable state are clear: we can study the properties of such a liquid experimentally as long as the necessary measurements can be made rapidly compared with the time required for the liquid to crystallize spontaneously.

The theoretical interpretation of experimental results obtained in this way would appear to be quite simple in principle. One sets up the phase space for the system in question. Certain regions of this phase space will correspond to regular geometrical arrangements of the molecules of the system. Such regions must be assigned to the various possible crystalline forms of the system. Let the volume of phase space enclosing these regions be labelled V_{cryst}. Other regions, much more extensive and of higher energy, will presumably be found which should correspond to the liquid form of the system. Call the volume included in these regions V_{liq}. Then it should be possible to derive the properties of both the supercooled and the normal liquid from the phase integral, or partition function (23, 52)

$$Q_{\text{liq}} = \frac{1}{N!h^{3N}} \int_{V_{\text{liq}}} \cdots \int e^{-H(p_1, \cdots, q_{3N})/kT} \, dp_1 \cdots dq_{3N}$$

$H(p_1, \cdots, q_{3N})$ being the energy at the point $p_1, \cdots, q_{3N}$ in phase space, and the integration being performed only over the volume V_{liq} "defined" above. Similarly, the properties of the crystalline phases may be calculated from

$$Q_{\text{cryst}} = \frac{1}{N!h^{3N}} \int_{V_{\text{cryst}}} \cdots \int e^{-H(p_1, \cdots, q_{3N})/kT} dp_1 \cdots dq_{3N}$$

where the integration is this time over the volume V_{cryst} of phase space.

If this procedure is applied either to the normal liquid above its freezing point (where $Q_{\text{liq}} \gg Q_{\text{cryst}}$) or to the crystal below its melting point (where $Q_{\text{cryst}} \gg Q_{\text{liq}}$), no difficulty should be encountered in specifying V_{liq} or V_{cryst}. In fact, in either case the integration could be carried out over the *entire* volume of phase space and we would expect to arrive at the same answer for all practical purposes. For we know that (except possibly at temperatures immediately above and below the melting points of some substances for which "premelting" and "prefreezing" phenomena have been claimed to occur) the inequalities of Q_{liq} and Q_{cryst} must be overwhelmingly one-sided.[1]

On the other hand, when applying this procedure to the supercooled liquid (for which $Q_{\text{liq}} \ll Q_{\text{cryst}}$), the correct identification of V_{liq} is of the greatest importance and may be quite difficult. We must be very careful to exclude all parts of V_{cryst} from V_{liq}, for even a tiny portion of V_{cryst} might contribute much more to Q_{liq} than the entire integral over the correct V_{liq}. Generally it should not be difficult to avoid such an error, for the crystalline regions of phase space are undoubtedly very easily detected by virtue of their great geometrical regularity. On the other hand, we can expect to encounter regions of phase space which are not obviously either crystalline or liquid-like. We may hope that such regions (which we shall refer to as "ambiguous" regions) either have very high energies, $H(p_1, \cdots, q_{3N})$, and hence very small values of $e^{-H/kT}$, or else have a relatively small extent in phase space; in either instance they should make a negligible contribution to the value of Q_{liq}. The regions of phase space corresponding to states near the tops of the free energy barriers which impede the

---

[1] The probability that a sample of ice will turn spontaneously into liquid water is $Q_{\text{liq}}/(Q_{\text{liq}} + Q_{\text{cryst}})$. Now

$$kT \log_e Q_{\text{liq}}/Q_{\text{cryst}} = F_{\text{cryst}} - F_{\text{liq}} \cong (\Delta H_m/T_m)\Delta T$$

where the F's are the free energies of the two forms of the sample, ΔH_m and T_m are the heat of fusion and normal melting temperature, and ΔT is the difference between the temperature of the sample and its normal melting point. For a 1-g. sample of ice at -1°C. it is found that

$$Q_{\text{liq}}/Q_{\text{cryst}} = 10^{-10^{20}}$$

formation of crystal nuclei will, for instance, be in this "ambiguous" region between V_{liq} and V_{cryst}.

In this paper we shall review and interpret the properties of supercooled liquids from this point of view. First we shall consider the rather peculiar "transition" to a "glassy" or "vitreous" state which all such liquids probably pass through when cooled sufficiently. Evidence will be presented to show that, as many workers have suggested, this "transition" is really a relaxation phenomenon arising from the slowness with which molecules change their positions below a certain temperature. As a result of this sluggishness of molecular motion, the liquid is unable to change its structure appreciably during the time required to measure various common liquid properties such as the specific heat, density, and compressibility. Now, a sizeable contribution to many of these properties should arise from the change in the structure of the liquid following a change in temperature or pressure. This contribution of changing liquid structure is, therefore, absent in glasses, and the phenomenon of glass formation provides us with a means of evaluating the contribution of liquid structure changes to the properties of the liquid. A survey of the pertinent data reveals that for many properties these contributions are considerable if not predominant in liquids at low temperatures.

Thus, in the glassy or vitreous state the liquid exhibits a new, more limited kind of metastability as compared with that of the normal supercooled liquid. The energy barriers supporting this metastability are those impeding changes in the positions of molecules in the liquid, and the phase integral of the glass is to be carried out over a volume of phase space, V_{glass}, which not only excludes crystalline configurations but also suppresses many configurations of the liquid which would otherwise become important at lower temperatures. The regions to be included in V_{glass} are even more difficult to specify than those in V_{liq}; in general, they will depend on the temperature at which the glass was formed—which, in turn, depends on the rate at which the liquid was cooled when it vitrified.

In the second part of the paper we shall ask how a liquid would be expected to behave at very low temperatures if experimental measurements were made sufficiently slowly to avoid glass formation—that is, slowly enough to permit the liquid structure always to be in thermodynamic equilibrium with the surroundings (but, of course, not so slowly as to permit spontaneous crystallization). It is reasonable to expect a clue to this behavior from a simple extrapolation to low temperatures of the known properties of supercooled liquids above their glass-transformation temperatures. When such an extrapolation is applied to the observed entropy *vs.* temperature curves of several substances (most strikingly with glucose and lactic acid), a rather startling result is obtained. Not very far below the glass-transformation temperature, but still far above 0°K., the extrapolated entropy of the liquid becomes less than that of the crystalline solid (see figure 4). The extrapolated heat content *vs.* temperature and specific volume *vs.* temperature curves show similar tendencies (see figures 3 and 6): the liquid appears to strive for a lower heat content and a smaller specific volume than the crystal at temperatures well above 0°K.

This peculiar result can only mean that somehow the above "reasonable" extrapolation is not permissible. The following resolution of the paradox is proposed: There is reason to believe that as the temperature is lowered the "ambiguous" regions of phase space intermediate between the definitely crystalline and definitely liquid regions begin to be able to contribute significantly to the partition function of the liquid. This means that the free energy barriers between the liquid and the crystal tend to become relatively small at low temperatures. In particular, the barrier to crystal nucleus formation, which tends to be very large just below the melting point, may at low temperatures be reduced to approximately the same height as the free energy barriers which impede molecular reorientations in the liquid and which have been shown to be responsible for glass formation. Under these circumstances crystal nuclei will form and grow at about the same rate as the liquid changes its structure following a change in temperature or pressure. In other words, the time required for the liquid to crystallize becomes of the same order as the time required for it to change its structure following some change in its surroundings. If, then, measurements are to be made on such a liquid before it has had a chance to crystallize, these measurements must also be made before the liquid can bring its structure into equilibrium with its surroundings. But this means, as we have seen, that the liquid will behave as a glass. Thus, as the temperature of a liquid is lowered one is ultimately forced to study it as a glass if one wishes to study it as a liquid at all. A non-vitreous stable liquid cannot exist below a certain temperature, and it is operationally meaningless to extrapolate the entropy, energy, and specific volume curves below that temperature, as we tried to do with such peculiar results.

In order to illustrate these general ideas a simple theory of liquid structure suggested by Mott and Gurney is reviewed. It is shown how, in terms of that theory, one obtains a "pseudocritical point" of the postulated kind between the crystalline and liquid states at low temperatures. The possibility of the existence of such a "pseudocritical point" should furnish an interesting test of the adequacy of any proposed general theory of the liquid state. Many current theories of liquids do not provide for this possibility.

II. THE GLASS TRANSFORMATION

A. Characteristics of the glass transformation

Crystalline glucose melts at 141°C. to an easily supercooled liquid phase whose thermodynamic properties at lower temperatures show an interesting behavior (see figure 1). As the liquid is cooled below room temperature its coefficient of thermal expansion drops rather abruptly by more than a factor of 3 and its specific heat decreases by nearly a factor of 2. These changes occur within a temperature range of about 20°C. The heat content and the specific volume, however, show no analogous abrupt changes; the "transition"—if we wish to call it that—involves no latent heat or volume change.

In table 1 are listed some typical materials which in the supercooled liquid or amorphous form show a similar behavior. Indeed, all supercooled liquids whose

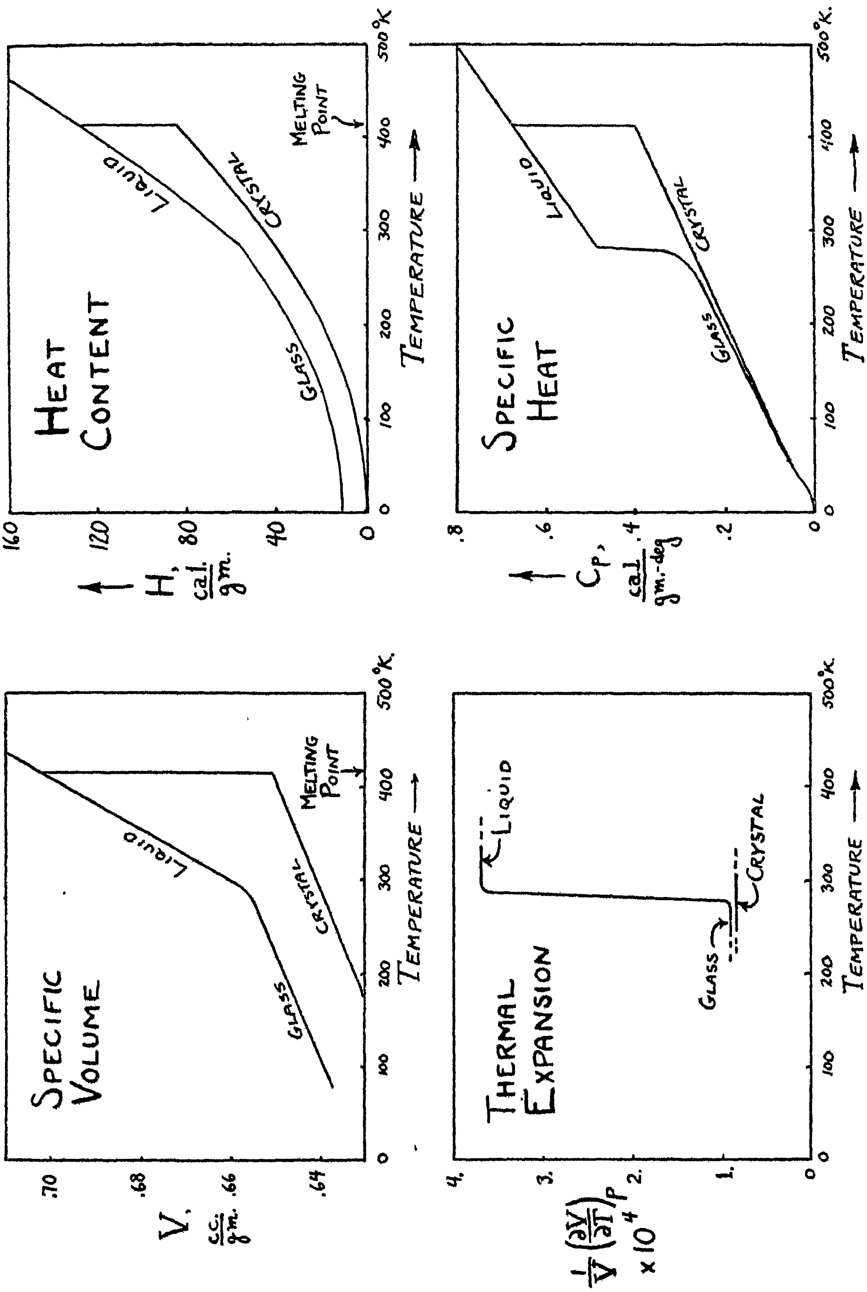


FIG. 1. Thermodynamic properties of glucose. Data from references 61, 67, 69 and 84.

thermal expansions or specific heats have been investigated in the appropriate temperature range seem to undergo a "transition" of this type, as do also practically all other amorphous materials for which no crystalline phase is known. That the occurrence of such a "transition" does not depend upon any very special chemical properties of the liquid is shown by the wide chemical diversity with which it may be associated. In table 1 we find hydrocarbons, strongly hydrogen-bonded liquids, a hydrated ionic compound, linear high polymers, and three-dimensional valence-bonded networks. Thus this behavior is probably a general property of the liquid or non-crystalline state of matter, and we may presume that it would be found for all liquids below their freezing points if the means were at hand to prevent their spontaneous crystallization during the necessary experimental measurements.

TABLE 1

Properties of liquids and glasses at their glass-transformation points

SUBSTANCE	T_g	SPECIFIC HEAT		COEFFICIENT OF EXPANSION × 10^4 (PER °C.)		REFERENCES
		Liquid	Glass	Liquid	Glass	
	°K.	cal./gram	cal./gram			
3-Methylhexane	80–90	0.397	0.17			(70)
2,3-Dimethylpentane	80–85	0.377	0.20			(70)
Ethanol	90–96	0.417	0.27			(31, 39, 63, 65, 166
1-Propanol	86–100	0.425	0.23			(65, 66)
sec-Butyl alcohol	100–115	0.397	0.20			(1, 70)
Propylene glycol	150–165	0.464	0.25	(6.2)	(2.0)	(65, 66)
Glycerol	180–190	0.456	0.25	4.83	2.4	(27, 65, 66, 79, 84)
d,l-Lactic acid	195–206	0.500	0.26			(70)
$Na_2S_2O_3 \cdot 5H_2O$	231			3.62	2.10	(79)
Sucrose	340			5.02	2.54	(79)
Glucose	280–300	0.51	0.33	3.7	0.90	(61, 67, 69, 84)
Boron trioxide	470–530	0.436	0.30	6.1	0.5	(79, 87, 88, 100)
Silicon dioxide	1500–2000	0.35?	0.30			(103)
Selenium	302–308	0.125	0.080	4.2 1.11	1.7 0.43	(55, 94, 96, 98)
Sulfur	244					(55)
Polyisobutylene	190–200	0.36	0.27	6.0	(0.5)	(19)
Rubber	200	0.39	0.27	6.0	2.0	(5, 6, 77, 81, 104)
Hycar-OR synthetic rubber	245–250	0.44	0.31			(7)
Polystyrene	353–363	0.44	0.30	5.9 4.5	2.1 2.7–2.8	(14, 71, 89)
Colophony	300	0.40	0.27	7.43 5.71 6.1	2.57 3.62 3.8	(79, 94, 96, 98)

The only crystalline substance for which a "transition" of this type has been observed seems to be one of the crystalline forms of cyclohexanol (40).

A non-crystalline material below the temperature at which such a "transition" takes place is said to be in the *glassy* or *vitreous state*. The material in that state is called a *glass*, and the temperature of the change is called the *glass-transformation point*. This temperature is frequently denoted by T_g. There is actually no sharply defined glass-transformation temperature, but rather a range of temperatures over which these changes occur; it would probably be better to use the term "glass-transformation interval." Ordinary window glass is the most common example of this state, but many other common materials, particularly among the natural and synthetic resins, are also normally used as glasses.

It is found that the values of the specific heat and coefficient of expansion of a glass are much closer to those of the crystalline form of the substance (where this is known) than to those of the parent liquid. This is well-illustrated by the data for glucose shown in figure 1. On the other hand, the structure of silicate glasses as revealed by x-ray diffraction studies (13, 74) is closely similar to typical liquid structures. Furthermore, the heat content and specific volume of the glass are continuous with the heat content and specific volume of the liquid. Apparently, then, the glassy state is a form of matter which maintains the structure, energy, and volume of a liquid, but for which the *changes* in energy and volume with temperature are similar in magnitude to those of a crystalline solid. That is, a glass is a liquid in which certain degrees of freedom characteristic of liquids are "frozen in" and can no longer contribute to the specific heat and thermal expansion. The problem presented to us by the glassy state is simply to determine what these degrees of freedom are and to explain how they are frozen in at the glass-transformation point, T_g.

B. Equilibrium and dynamic mechanisms in the glass transformation

This freezing-in of the liquid degrees of freedom in glass formation might be caused by either of two entirely different mechanisms. These are best explained by means of examples.

Equilibrium or *thermodynamic freezing-in* of a degree of freedom in some temperature range may be illustrated by the decrease in the specific heat of hydrogen gas between 300°K. and 50°K. owing to the disappearance of the contribution of the rotational degrees of freedom of the hydrogen molecule. Another illustration might be the well-known transition in ammonium chloride crystals at about 245°K., in which the rotation of the ammonium ion is believed to cease below the transition temperature (72). Here, however, the rotational degrees of freedom are presumably replaced by vibrational degrees of freedom, so that the specific heat below the transition region is not markedly lower than that at higher temperatures.

Dynamic or *relaxation freezing-in* of a degree of freedom may be illustrated by the behavior with decreasing temperature of the dielectric constant of a dipolar liquid (e.g., glycerol) as measured by an oscillating electric field of some specified frequency. The rotational degrees of freedom of the dipoles make their maximum contribution to the dielectric constant only if the dipoles are able to change their positions more rapidly than the oscillating field changes its direction. As the temperature is lowered, however, the rate of change of position of the dipoles rapidly decreases because of the increasing viscosity of the liquid. Ultimately a range of temperatures is reached in which the rotation rate becomes equal to and then much slower than the frequency of the applied field. Over this temperature range the dielectric constant loses the contribution of the rotational degrees of freedom of the dipoles, finally assuming its "optical" value at low temperatures.

Another example of relaxation freezing of degrees of freedom is in the measurement of the specific heats of gases by determination of the velocity of sound in the gas. If sound waves of too high a frequency are employed, certain of the vibrational degrees of freedom of the gas molecules may not have sufficient time to come into equilibrium with the fluctuating temperatures in the sound wave. They will then not be able to contribute to the effective specific heat, which will therefore seem to have a lower value than that found with slower methods of measurement.

These two mechanisms are fundamentally distinct. The thermodynamic mechanism arises from a structural change in the system or from the quantum-mechanical discreteness of its energy levels; it is an equilibrium phenomenon. The relaxation mechanism, on the other hand, is a consequence of a deficiency in the experimental procedure: it results from changing the external forces acting on a system and then making measurements before the system has had time to reëstablish complete thermodynamic equilibrium with its changed surroundings.

Experimentally we can in principle distinguish between the two mechanisms very simply: If some degree of freedom seems not to be contributing to a property of a system when a certain time is allowed for equilibrium to be reached, we merely prolong the equilibration time more and more and seek the limiting value of the property as the equilibration is extended for an indefinitely long time. If this limiting value is less than that expected from the full participation of all of the degrees of freedom of the system, then the thermodynamic mechanism must be operating. Otherwise we are dealing with a relaxation effect.

Such tests have been applied to a number of the substances listed in table 1. The results seem to indicate that glass formation is a relaxation effect, a view which is now widely held and which we shall assume to be correct (see Simon (85), Littleton (50), Richards (75), Jenckel (33), Morey (56), Kuhn (45), Ueberreitter (101), Alfrey, Goldfinger, and Mark (2), Simha (83), and Spencer and Boyer (89)). It must be admitted, however, that because of the enormous temperature coefficient of the relaxation rate leading to glass formation, the test is not always or even usually easy to apply unequivocally, so that, strictly speaking, there is a remote possibility that some of the substances listed in table 1 may really show a thermodynamic transition into a glass-like state.

It has been pointed out, especially by Boyer and Spencer (11) (see also Gee (25)), that the glass transformation has more or less the characteristics specified by Ehrenfest for a second-order transition. That is, the two "phases" involved differ in the second derivatives of the free energy, F, with respect to temperature and pressure, but not in the free energies themselves or in their first derivatives.

Thus the volume $V = (\partial F/\partial p)_T$ is unchanged in the transition but the coefficient of expansion

$$\alpha = \frac{1}{V}(\partial V/\partial T)_p = \frac{1}{V}(\partial^2 F/\partial p\, \partial T)$$

does undergo a rather sudden change; similarly the enthalpy

$$H = F - T(\partial F/\partial T)_p$$

is unchanged but the heat capacity

$$C_p = (\partial H/\partial T)_p = -T(\partial^2 F/\partial T^2)_p$$

undergoes a rather sudden change. Since, however, these considerations apply only to systems in thermodynamic equilibrium, it does not seem desirable to refer to the glass transformation as a second-order transition, unless it is intended to imply that a thermodynamic mechanism for the freezing-in of degrees of freedom is involved in the sense discussed above.

Similarly it might be desirable to restrict the term "glassy or vitreous transformation" to those changes in liquids in which relaxation effects are predominant. Thus we may define a glass as an amorphous or non-crystalline material in which certain internal degrees of freedom characteristic of the liquid state have not had time to come into thermodynamic equilibrium with their surroundings. The glass-transformation temperature, T_g, could then be "defined" in a very general way as the temperature below which the relaxation time for some degree of freedom is long compared with the duration of an experiment. Obviously, according to this "definition" the value of T_g might depend in an essential way on (*1*) the property or properties studied in the experiment, (*2*) the duration of the experiment, and (*3*) what we mean by a long time. With regard to the first of these factors, it is clear that we have *a priori* no reason to expect that, for instance, the relaxation rates of a liquid will be exactly the same for thermal expansion as for dielectric polarization or mechanical deformation. Surely the detailed molecular processes resulting in an increase in the volume of a liquid following an increase in its temperature are not quite, if at all, the same as those occurring on application of an electric field or a mechanical force. Therefore, we may expect the relaxation rates, and hence the value of T_g, to depend on the property being measured.

We see that any attempt at a precise definition of T_g requires the entirely arbitrary specification of conditions which are never mentioned or even implied in the definition of, say, a thermodynamic melting point. It does not seem desirable to attempt such a precise definition of T_g. Instead, we shall proceed to define it on more convenient though admittedly somewhat arbitrary lines.

We have seen that it is both convenient and customary to detect the occurrence of a glass transformation by means of specific heat and thermal expansion measurements. Therefore it is natural to define the glass-transformation temperature in terms of these two properties alone. Furthermore, the conventional measurements of specific heats and coefficients of thermal expansion generally allow times of the order of several minutes to 1 hr. for equilibrium to be established. Thus in a more limited but more convenient and conventional sense we may define the glass-transformation point of a liquid as *that temperature at which the specific heat or the thermal expansion coefficient of the liquid shows a more or less sudden change due to relaxation effects in experiments allowing something like 10 min. to 1 hr. for equilibrium to be reached.*

C. Identification of the molecular motions involved in the glass-relaxation process

Insofar as we are justified in regarding glass formation as a relaxation process, the problem of the nature of the glassy state may be stated in the form of two questions: (*1*) What are the molecular movements which are so slow in glasses? (*2*) How do these motions contribute to the specific heat, thermal expansion, and other properties which differ in glasses and liquids?

The key to the answer to the first of these questions is to be found in the four following facts: (*a*) T_g as determined by specific heat measurements is always very nearly the same as T_g from coefficients of expansion. (*b*) The temperature coefficient of the relaxation rate in glass formation is very large. (*c*) At T_g the relaxation time for dielectric polarization is of the order of several minutes to an hour. (*d*) Liquids at their T_g have viscosities of about 10^{13} poises.

(*a*) *The near identity of the T_g's from specific heats and expansion coefficients* is illustrated by the data for glucose shown in figure 1 and is implied in the manner of presentation of the data of table 1. This fact is significant even though it may not be too surprising, since there is no reason in principle why the relaxation rates for changes in heat content and volume should be related. *Apparently the molecular motions involved in the readjustment of the liquid energy and of the liquid volume following a change in temperature are closely similar.*

(*b*) *The rapid change in the relaxation rate with temperature* is illustrated by some results of Jenckel (33), who found that the half-time for the equilibration of the density of amorphous selenium following a change in the temperature varies from 5 min. at 35°C. to 130 min. at 30°C. Spencer and Boyer (89) have made a similar study on polystyrene and found half-times to vary from 25 min. at 90°C. to 13.6 hr. at 30°C.

Indeed, the strong dependence of the relaxation rate on the temperature is the cause of the apparent abruptness in the change in the specific heat and coefficient of expansion around T_g which has led some workers to believe that the glass transformation is thermodynamic in nature. The range of temperatures over which these changes occur is determined by the difference between the temperature at which the relaxation process just becomes noticeable during a measurement and the temperature at which this relaxation becomes negligible in the same time. Let us assume that the change in any property, P, with time, t, following some change in external conditions obeys a unimolecular law, $P_e - P = \Delta P \exp(-kt)$, where P_e is the final equilibrium value of P, k is a rate constant, and ΔP is a constant. (As will be discussed further below, the observed glass relaxation usually does not follow such a unimolecular law very well.) If we more or less arbitrarily say that the relaxation process is negligible at the end of a time t at temperature T_1 when $(P_e - P)/\Delta P = 0.9$ (corresponding to $k_1 t = 0.105$), and is essentially completed in the same time at another, higher temperature T_2 when $(P_e - P)/\Delta P = 0.1$ (corresponding to $k_2 t = 2.30$), then $k_2/k_1 = 21.9$. That is, between T_1 and T_2 the relaxation rates change by something of the order of twentyfold. For glycerol this change requires a temperature interval of about 10°C.

It is clear that the relaxation rate undoubtedly depends exponentially on the temperature. Therefore, by well-known arguments we may conclude that *the relaxation process involves the passage of the relaxing unit over a potential energy barrier very considerably higher than the mean thermal energy.*

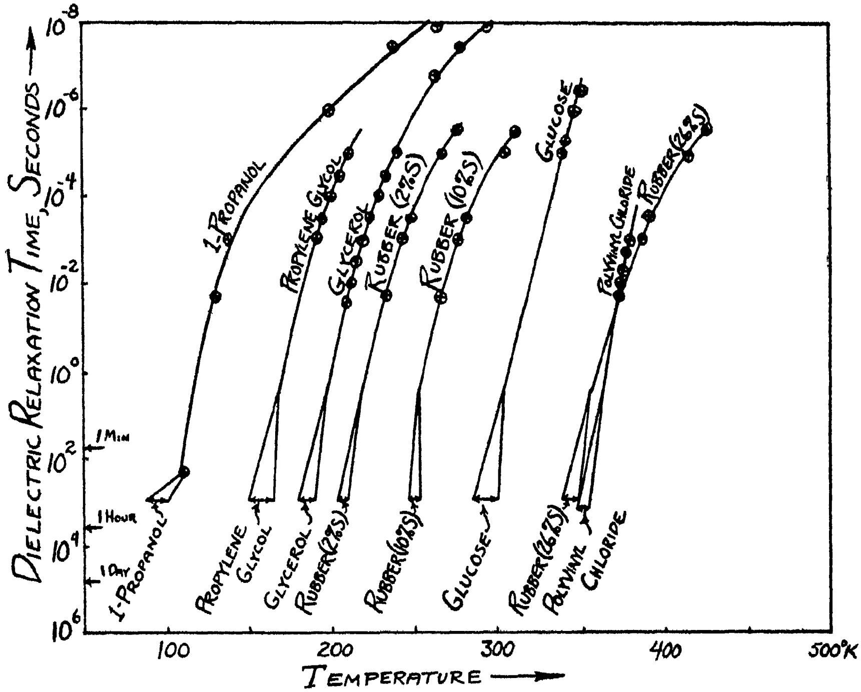


FIG. 2. Relationship between dielectric relaxation times and glass-transformation temperatures. Horizontal arrows indicate the range of the observed T_g. Data from table 2 and reference 36.

(c) *The close relationship between dielectric relaxation and the glass transformation* is indicated in figure 2, where the temperature dependence of the dielectric relaxation times of a number of glass-forming liquids is shown, along with an indication of the temperature range in which the glass transformation is observed to take place. In all examples except possibly 1-propanol a reasonable extrapolation yields dielectric relaxation times of the order of a few minutes to an hour at the glass-transformation point. This result means that *the relaxation process leading to glass formation involves molecular motions closely related to those performed by dipoles (and by inference then also by any molecules) when they jump from one equilibrium orientation to another owing to thermal agitation.*

(*d*) It has been widely noticed that *liquids at the glass-transformation point have viscosities near* 10^{13} *poises* (19a, 32, 64, 68, 78, 95). The significance of this fact becomes clear when considered from the point of view of Eyring's theory of viscous flow (18). According to this theory the viscosity, η, of a liquid whose flow is Newtonian can be given in terms of the rate, k_0, at which its molecules jump from one equilibrium "lattice position" in the liquid to another by

$$\frac{1}{\eta} = \frac{\lambda^2 A}{lkT} k_0$$

where k is Boltzmann's constant, T is the absolute temperature, λ and l are lengths of the order of molecular dimensions, and A is of the order of such dimensions squared, so that $\lambda^2 A/l \cong V/N$, where V is the mole volume and N is Avogadro's number. Thus we can obtain an approximate expression for the molecular jump rate k_0 in terms of the viscosity:

$$k_0 \cong RT/V\eta$$

If V is 30 cc., T is 300°K., and η is 10^{13} poises, k_0 turns out to be about one jump every 3 hr., which, considering the approximations we have made, is about the same as the expected relaxation rate at T_g.[2]

Evidently the relaxation processes in glass formation have close similarity to the molecular processes in viscous flow. Furthermore, in the light of Eyring's theory of viscosity, these processes probably involve jumps of molecular units of flow between different positions of equilibrium in the liquid's quasicrystalline lattice.

From these four facts we must conclude that the relaxation processes in glass formation are of a rather general type. Their similarity to the molecular processes in dielectric relaxation and viscous flow is particularly interesting, since a good deal of information is available concerning the mechanisms of these proc-

---

[2] We may also in this connection make use of Einstein's theory of rotational Brownian motions (17), according to which the mean time required for a molecule to change its orientation by an angle of θ radians is

$$\tau_\theta = \frac{\theta^2}{2} \cdot \frac{4\pi\eta r^3}{kT}$$

where r is the radius of the molecule (assumed to be spherical) and η is the viscosity of the surrounding medium (assumed to be the macroscopically observed viscosity). If we write $V/N = 4\pi r^3/3$ = molecular volume as before, we find

$$\tau_\theta = \frac{3\theta^2 V\eta}{2RT}$$

or for the rate of relaxation

$$k_\theta = \frac{2}{3\theta^2} \frac{RT}{V\eta}$$

Except for the factor $2/3\theta^2$ this is similar to the result from Eyring's theory. Presumably a rotation of a molecule by about one radian is, according to the Einstein theory, about as frequent an occurrence as a jump by a molecule from one equilibrium position to another in the liquid according to the Eyring theory.

esses. It would appear that, particularly in liquids far below their boiling points, there exists a considerable amount of short-range quasicrystalline order. Because of this the positions and relative orientations of neighboring molecules are rather rigidly fixed, so that a change in the position of any one molecule requires simultaneous relatively drastic changes in the positions of all of its neighbors. As a result, molecular motions of any kind in such liquids lead to a considerable temporary local disruption of the liquid structure. This accounts for the very large positive entropies of activation which are observed for viscous flow and dielectric relaxation in many amorphous substances at low temperatures (36). It also accounts for the following rather remarkable fact.

A number of very different kinds of molecular motions may occur in liquids: Molecules may rotate about some axis as in dielectric relaxation, they may move to new lattice sites as in diffusion, and they may move past one another in local shearing motions as in viscous flow. These movements are quite dissimilar, and yet they all seem to occur at about the same frequency. We can account for this by supposing that in order for *any* kind of molecular movement to occur in a liquid, a definite amount of temporary disruption of the liquid structure must occur in the neighborhood of the moving molecules. Once this disruption has occurred, one kind of movement is about as easy to perform as any other. It is, therefore, not too surprising that the molecular movements involved in glass formation have turned out to belong in this same general class.

D. Identification of the degrees of freedom involved in the glass transformation

Having answered the first of the two questions concerning the nature of the glassy state, we must now consider the second: How do these molecular motions influence those physical properties which differ in glasses and liquids? What are the degrees of freedom which do not contribute to the thermodynamic properties of vitreous liquids and how do they involve the ability of molecules to change their positions?

It is often suggested that the degrees of freedom in question are the momenta associated with the changing positions of the molecules. By this it is implied that, for instance, the drop in the specific heat below T_g may be due to the cessation of the "free rotation" of molecules and of parts of molecules. This cannot possibly be the case. At temperatures just above the glass-transformation point we have seen that the dielectric relaxation times of polar liquids are of the order of seconds. This can be interpreted to mean either that the molecules rotate extremely slowly or, better, that at any instant only very few freely rotating molecules are present. From either point of view the kinetic energy associated with the freely rotating molecules must be extremely small and their contribution to the specific heat must be entirely negligible.

That the mere ability to make relatively infrequent changes in equilibrium position during an experimental measurement does not by itself lead to any appreciable contribution to the specific heat or thermal expansion is clearly shown as follows: The self-diffusion of lead atoms in solid lead at a temperature T is known to be given by a diffusion constant (4):

$$D = 5.1 \times 10^{-6110/T} \text{ cm.}^2\text{/sec.}$$

It is easily shown (82) that the diffusion constant can be expressed in terms of k_0, the number of jumps per second of atoms between lattice points, and λ, the distance between those points, by $D = k_0\lambda^2$. If λ is 3 Å., then $\log_{10} k_0 = 15.8^{-6110/T}$, and it is found that k_0 for lead atoms is one jump per second at 114°C. and one jump per day at 23°C. Thus if simply the ability of atoms to jump several times during an experiment could give rise to a contribution to the specific heat or the thermal expansion, lead would show a glass-like transformation somewhere between 20° and 120°C. Of course, no such transformation is observed. Similarly, Murphy (60) observed that the dielectric relaxation time of ice becomes of the order of hours at 130°K., but Giauque and Stout (26) found no significant glass-like transformation in ice between 15°K. and 273°K.

A clear distinction exists, therefore, between liquids and crystalline solids in this respect. The reason for this distinction was first pointed out by Simon (85). When the temperature of a simple crystal is changed, only the amplitudes of the very nearly harmonic oscillations of the atoms and molecules making up the lattice are affected. No changes in the crystal structure occur requiring that the molecules be reshuffled among their lattice positions. Therefore the inability of the molecules to move about in the lattice of a crystal during an experiment has no effect on the thermodynamic properties of the crystal. On the other hand, as the temperature of a liquid is changed, the liquid structure changes in a relatively drastic way. Thus the average coördination number and the extent of the short-range order both decrease as the temperature is raised (8, 8a, 57, 73). But the coördination number of any particular molecule in a liquid can change only by whole numbers, and the short-range order in any particular microscopic region must vary by similarly discrete steps. Each such change must require a relatively drastic rearrangement in the positions of, say, a dozen or so molecules relative to one another. Such rearrangements can only occur if molecules are free to move from one equilibrium position to another—i.e., if molecules are capable of making movements of just the sort which we have already shown to be involved in the glass transformation.

Accompanying these structural changes in the liquid there are energy and volume changes which, since they occur continuously as the temperature is changed, appear as contributions to the specific heat and thermal expansion. It must be these contributions which disappear below the glass-transformation point. The degrees of freedom which are ineffective in glasses are therefore undoubtedly exclusively configurational and do not involve momenta at all; glass formation probably affects the potential energy term of the Hamiltonian of the liquid, not the kinetic energy term.

E. Interpretation according to the hole theory of liquids

Any further discussion of the degrees of freedom involved in glass formation must be in terms of some particular theory of liquid structure. It is interesting to try to interpret the phenomena at T_g in terms of the hole theory of liquids.[3]

---

[3] The possible rôle of holes in glass formation was suggested by T. Alfrey, G. Goldfinger, and H. Mark (2).

According to one form of this theory, a liquid is a quasicrystal with some of the lattice points occupied by molecules and others not occupied at all—that is, they are occupied by holes. The best evidence for this theory is probably the law of Cailletet and Mathias, according to which the mean densities of the liquid and vapor of many substances are independent of the temperature when these two phases are in equilibrium with each other. This was interpreted by Eyring (18) to mean that as the temperature is raised and molecules go from the liquid into the vapor, the space in the liquid formerly occupied by the vaporized molecules is not taken up by other molecules but remains as holes of size equal to that of a vaporized molecule. The observed decrease in density of the liquid with increasing temperature is thus largely due to the introduction of holes into the liquid and only slightly due to increased amplitudes of molecular oscillations such as cause the thermal expansion of crystals. The energy required to form such a hole is of course the latent heat of vaporization. As the temperature is raised and holes are introduced energy must be supplied, so that there is a contribution of the holes to the specific heat of the liquid.

Now the introduction of holes must require a considerable rearrangement of molecules among new equilibrium positions. If these rearrangements cannot occur during the duration of an experiment, the contribution of the holes to the specific heat and thermal expansion cannot be made.[4] Then, according to the hole theory of liquid structure, the drop in specific heat and thermal expansion at T_g is equal to the contribution of holes to these properties at that temperature. Let ΔC_p be the change in the specific heat (in units of calories per gram per degree) at T_g, and let $\Delta\alpha$ be the change in the coefficient of expansion (in units of cubic centimeters per cubic centimeter per degree). Then the volume of holes introduced into 1 cc. of the normal liquid above T_g by a change of temperature ΔT is $\Delta\alpha\Delta T$ cubic centimeters. The energy required to form this volume of holes is $\rho\Delta C_p\Delta T$ cal., where ρ is the density of the liquid. The energy required to form 1 cc. of holes is thus $\rho\Delta C_p/\Delta\alpha$. On the other hand, as a consequence of Eyring's arguments, the product of the heat of vaporization per gram and the density, $\rho\Delta H_{\text{vap}}$, is the energy required to form 1 cc. of holes having the sizes and shapes of the molecules of which the liquid is composed—that is, holes of the type known to occur at temperatures for which the Matthias–Cailletet law is valid. Clearly, if the holes which exist in supercooled liquids are of the same type as those occurring near the critical point, $\Delta C_p/\Delta\alpha$ should be approximately equal to ΔH_{vap}.

Values of $\Delta C_p/\Delta\alpha$ and estimated values of ΔH_{vap} are given in table 2 for all liquids for which the necessary data exist. Apparently several times as much energy is required to form a given volume of holes around T_g as to form the same volume of holes each having the same size and shape as a molecule. This could be interpreted to mean that the holes at these low temperatures are much smaller than entire molecules, since it would be expected that considerably more energy would be required to form, say, four quarter-sized holes than one full-sized one because of the larger surface which is involved. Such an interpretation is, however, incompatible with the usual and attractive concept of holes as empty lattice sites, and we are led to suspect that the hole theory may not be very useful when applied to liquids at very low temperatures.

---

[4] Alfrey, Goldfinger, and Mark speak of the holes as diffusing into the sample from its surface. If this diffusion is to be interpreted as occurring in the same way as ordinary molecular diffusion, with the hole moving only between adjacent lattice sites, then the rate of volume change following a change in temperature—and hence the value of T_g—will depend on the size and shape of the specimen. This seems unlikely. On the other hand, it is quite possible that holes can appear directly at any point in the liquid, resulting in a corresponding expansion of the liquid as a whole. In a sense the hole has still "diffused" in from the surface, but the mechanism is altogether different from that ordinarily associated with diffusion.

TABLE 2

Comparison of the heat of vaporization with the energy required to introduce holes into liquids at low temperatures

SUBSTANCE	ΔC_p	$\Delta\alpha \times 10^4$/ DEGREE	$\Delta C/\Delta\alpha$	ΔH_{vap}*
	cal./degree/ gram			*cal./gram*
Glycerol	0.27	2.4	1100	250
Propylene glycol	0.26	4.3	600	250
Glucose	0.18	2.8	640	200
Selenium	0.045	0.68–2.5	180–660	390
Rubber	0.12	4.0	300	100
Polyisobutylene	0.11	5.5	200	100
Polystyrene	0.14	1.8–3.8	370–780	90

* Estimated from heats of vaporization of volatile materials of similar structure, using Trouton's rule if necessary.

F. Effect of vitrification on properties other than the thermal expansion and the specific heat

The *compressibility* would be expected to decrease in the same way as the thermal coefficient of expansion at T_g, since the structural contribution to the volume should depend on the pressure as well as on the temperature. The only available information on the compressibilities of non-polymeric glasses above and below T_g is due to Tammann and Jellinghaus (96), who found increases in the compressibility of 60 per cent for salicylin glass, of 33 per cent for selenium glass, and of 68 per cent for colophony glass on going above the respective glass-transformation temperatures. Scott (81) found similar changes for rubber at its transformation point. Tammann and Jenckel (97) found that if materials which form glasses are cooled under pressure from above the glass-transformation point, they maintain an abnormally high density when the pressure is released. Thus, they were able to prepare samples of boron trioxide glass having densities of from 5 per cent to more than 7 per cent above normal by subjecting boron trioxide to a pressure of 5700 kg./cm.^{2} above 250°C. and cooling under this pressure to room temperature. These strikingly large density increases disappeared on raising the temperature close to T_g under normal pressure. Clearly in these experiments the abnormal density is due to forcing holes or other structural features tending to lower the density out of the sample at a temperature at which the molecules are still mobile, and then only releasing the pressure at temperatures so low that the density-lowering structures cannot be reformed in the material.

There is evidence from both Scott's and Tammann's results that increasing the pressure increases T_g. Similarly, Kobeko and Shushkin (44) have reported that the glass-transformation temperature of a mixture of phenolphthalein and salol can be raised 50°C. by applying 6000 atm. of pressure. Since increasing pressures would be expected to slow down the relaxation processes at a given temperature, this effect is in the expected direction according to our view. Such an effect on the viscosity is well known, and Danforth (15) found that the dielectric relaxation time of glycerol was increased by high pressures. On the other hand, it should be mentioned that Gee (25), considering the glass-like transformation in rubber as a true thermodynamic transition of the second order, has been able to show that the observed effect of pressure on the transition temperature in rubber is of the order of magnitude expected from Keesom's equation (38) for the effect of pressure on the temperature of a second-order transition,

$$(\partial T/\partial p) = TV\Delta\alpha/\Delta C_p$$

where T is the transition temperature, V is the specific volume, and $\Delta\alpha$ and ΔC_p are the changes in the expansion coefficient and specific heat at the transition.

The *thermal conductivity* of a condensed phase is determined by the anharmonicity of the intermolecular potential and by the regularity of the arrangements of the molecules (9), so it should not depend very much on the ability of the liquid to change its structure. Therefore, no significant change in this property is to be expected at T_g. This is essentially confirmed for glucose by Green and Parks (28) and for rosin and phenolphthalein by Kuvshinski (46). On the other hand, Schallamach (80) has obtained some very strange results for the thermal conductivity of rubber in the vicinity of its T_g. In agreement with Green, Parks, and Kuvshinski, he was able to cool rubber as much as 100°C. below T_g without noticing any discontinuity in the temperature dependence of the thermal conductivity. At sufficiently low temperatures, however, there was a sudden drop in the conductivity accompanied by a "clicking noise." On reheating the conductivity remained low up to T_g, where it increased rapidly to its normal value. It is questionable if this behavior has any significant bearing on the glass transformation, however.

According to Roseveare, Powell, and Eyring (76) the *viscosity* of a liquid should depend in part on how many holes are present in the liquid, being lower the greater the number of holes present. We should, according to this view, expect the viscosity–temperature curve to show some effects of the freezing-in of an excess number of holes below T_g. Such an effect is indeed observed in the silicate glasses (48, 49, 91) and in glucose glass (68), the viscosity below T_g being abnormally low as compared with the values expected from the extrapolation of data taken above T_g. The viscosity just below T_g is also observed to increase with the passage of time by as much as a factor of 10 or more, presumably because the holes, etc., gradually seep out of the specimen on standing.

All liquids have *elastic rigidity moduli*, but it is only when their viscosities are high that it becomes possible to measure them by the usual techniques. Such a modulus should certainly depend in part on the change in liquid structure under external stress for the same reason that the compressibility depends in part on this property. Therefore the modulus, if measured by the usual "slow" methods, should change around T_g. Parks and Reagh (68) found a rapid decrease in the torsion modulus of supercooled glucose threads above T_g. The high-temperature value of the modulus was only about one-twentieth of that found below T_g. Taylor (99) was able to observe a time-dependent portion of the elastic moduli of several silicate glasses in a limited temperature range near T_g. Kobeko, Kuvshinski, and Gurevich (42) made detailed studies of the time dependence of the elastic deformation of rosin, phenolphthalein glass, and rubber as a function of the temperature near the glass-transformation point and found a time-dependent decrease in the modulus near T_g. For phenolphthalein and rosin there is a difference of about tenfold between the "slow" (temperature above T_g) and "fast" (temperature below T_g) moduli.

Although a very considerable change in elastic properties of the simple glasses thus usually takes place at T_g, the long-chain polymeric glasses show even greater changes. This, of course, is because of the possibility of long-range elasticity in polymers, a phenomenon which is entirely dependent on the ability of the polymer to change its molecular configuration during the course of the experiment. Thus the results of Meyer and Ferri (53) show that the onset of long-range elasticity in rubber containing 8 per cent sulfur as the temperature is raised occurs at approximately the glass-transformation point, as observed by Kimura and Namikawa (41) for rubber containing this amount of sulfur. Even more clear are the results of Alexandrov and Lazurkin (1), who measured the elasticity of rubber and other polymers when subjected to periodic stresses of frequencies varying between 1 min.^{-1} and 1000 min.^{-1} If their results on rubber are extrapolated to frequencies of 1/10 min.^{-1} to 1/100 min.^{-1} (equivalent to experiments lasting from several minutes to an hour or so; *cf.* the treatment in figure 2 for dielectric relaxation), it is found that the elasticity undergoes a large increase (equivalent to the onset of long-range elasticity) at approximately the same temperature as T_g.

G. The kinetics of vitrification

One might expect that the relaxation processes in glass formation would follow an exponential decay law such as was set forth earlier in this paper. This is often found not to be the case. Jenckel (33) found that the change in volume following a change in temperature is exponential in the square root of the time. Boyer and Spencer (10) propose a hyperbolic tangent law based upon Eyring's equation for non-Newtonian flow. Lillie (49) found that the viscosity changes with time according to the relation

$$d\eta/dt = k(\eta_0 - \eta)/\eta$$

where k is a constant and η_0 is the viscosity reached at equilibrium. Taylor (99), on the other hand, finds a simple exponential law to be adequate for the time-dependent portion of the elastic deformation of silicate glass, and Boyer and Spencer (10) found the same for the volume change of polystyrene.

The situation would seem to be very similar to that in dielectric relaxation, where it is also found that the unimolecular decay law is not followed. In the case of dielectric relaxation the reason for this seems to be that there is no single relaxation time, but rather a whole distribution of them (24). This may include rates which differ by many powers of 10, so causing the relaxation to be spread out in time much more than would be expected according to the unimolecular law. This spreading-out of the relaxation process is characteristic of all of the empirical expressions referred to above, so there is good reason to believe that a similar complication exists here. Indeed, according to the explanation which has been offered for the distribution of dielectric relaxation times (36), it would be surprising if such a distribution did not occur in glass formation.

Although we have been stressing the similarity between the various relaxation processes involved in glasses, it is worth pointing out that these similarities probably do not extend to complete identity. Thus the details of the kinetics of the change in volume following a change in temperature will probably not be found to be identical with the elastic relaxation following a change in stress or the change in dielectric polarization following a change in the applied electric field. A detailed study of these differences might prove quite interesting.

H. Usefulness of glasses in theoretical investigations of the liquid state

We have seen that the glass transformation provides us with the means of separating the effects of changing liquid structure on various properties from the other factors involved in these properties. This separation is only possible at those temperatures at which the relaxation times are of the same order as the duration of the experiment. It would be desirable, however, to study the change in this contribution as the temperature is altered. This can be done, as we have seen, by changing the duration of the experiment, but for many properties we are not free to change equilibration times by a very large amount. This is unfortunately especially true of calorimetric measurements. Measurements of thermal expansion can be made over indefinitely long times but cannot be made with equilibration times shorter than 1 or 2 min. It is in this connection, however, that measurements using sound would be particularly useful (75). Depending on the experimental arrangement, the velocity of sound waves will depend on the shear modulus or on the compressibility of the medium through which they pass, so that from the measured velocity of such waves the shear modulus and the compressibility could be found. Just as the contributions of rotating dipoles to the dielectric constant can be separated from the contributions of atomic and electronic polarization by comparing dielectric constants obtained with electromagnetic waves of very low and very high frequencies, so the contribution of changing liquid structure to the compressibility and to the shear modulus could be separated from the contributions of the other factors by studying the sound velocity over a wide range of frequencies. Thus, sonic and ultrasonic methods coupled with extended static experiments might make possible the analysis of the elastic properties of liquids into their two components over a fairly considerable range of temperatures.[5] Important steps in this direction are being made by Mason (51).

When a substance can be prepared in both crystalline and supercooled forms, however, a much simpler means of separating the two contributions is open to us over a limited range of temperatures. We have seen that certain properties of glasses have values very close to those of the crystalline solid. Therefore, we have merely to measure the property for the crystal and for the supercooled liquid, subtract the one from the other, and obtain very closely the contribution of the changing liquid structure to that property. This procedure should work well for the specific heat, coefficient of expansion, and compressibility at all temperatures between the melting point and T_g.

I. Concept of torpid states of matter

The glassy state of liquids is only a single example of a more widespread condition in which matter has been compelled to change its state too rapidly for its structure to remain in normal equilibrium. Because a certain sluggishness is implied in such behavior, matter in such a condition might be said to be in a *torpid state.* For example, when metals and other crystalline solids are plastically deformed at relatively low temperatures, their structures change because the applied stress makes possible movements of atoms which under equilibrium conditions would practically never be tolerated. After severe plastic deformation of such crystals their x-ray diffraction patterns are markedly altered and their lattice energies and plastic properties are changed ("work hardening"). If the same amount of deformation were permitted to take place sufficiently slowly, on the other hand, the crystal would presumably be able to retain its normal structure and other properties. Crystals in this so-called "work-hardened" condition, like glasses, are in a torpid state.

(1) A limitation of the Eyring relation for plastic flow

It seems likely that whenever in plastic deformation the external forces compel the molecular units of flow to move much more rapidly than they normally would under the influence of thermal fluctuations, some kind of temporary or permanent changes in the plastic properties can be expected. This is easily seen in terms of Eyring's expression for the rate of shear as a function of the applied stress. According to Eyring (18)

$$\text{Rate of shear} = K[\exp(af) - \exp(-af)] = 2K \sinh af$$

where K is a constant and af is the ratio to the mean thermal energy, kT, of the work done by the external stress, f, in pushing the flow units into the activated state. The first exponential in this expression arises because the external forces do work in *lowering* the activation energy barrier for molecular shear processes tending to relieve these forces. The second exponential arises because the external forces do work in *raising* the activation energy barrier for the molecular processes in the opposite direction. When af is small, that is, when the activation energy is supplied chiefly by thermal fluctuations, $\sinh af \cong af$ and we have ordinary Newtonian flow. When, on the other hand, most of the activation energy is supplied by the external forces, so that $af \gg 1$, the second exponential in the hyperbolic sine becomes negligible and $\sinh af \cong 1/2 \exp(af)$. Flow according to this law is observed in the creep of metals (16, 35), textile fibers (29, 30), and other materials. Evidently in this type of flow those particular molecular motions which result in a change of shape of the specimen tending to relieve the applied stresses will be very much more frequent than other types of molecular motion. Furthermore, any "backtracking," represented by the second term in the hyperbolic sine expression, will be definitely discouraged. Now among the former "forward" types of motions, it may happen that some lead to a situation analogous to a "blind alley" or to a "traffic jam." That is, certain types of motion of the units of flow may result in entanglements such that further forward movements of these flow units become impossible. In order for the entanglements to become unsnarled we might expect that the flow units may under some conditions first have to "backtrack." If this is the case, then the suppression of the backtracking movements by the external forces will lead to a work hardening of the material which will make the Eyring expression inapplicable without some modification.

---

[5] A change in equilibration times by a factor of 10^9 could easily be accomplished in this way.

Such a possibility is especially evident in the flow of linear polymers. Here it seems very likely from Flory's work (20, 37) that the flow takes place by the successive movements of relatively short segments of the entire molecule. Many of these motions, however, undoubtedly result in severe entanglements of different chains very similar to the knots and interpenetrating loops which occur in a badly snarled mass of string which one has tried to disentangle by merely pulling on a few loose ends. These entanglements are probably most easily undone if the segments are given time to retrace their movements at least partially and try again in some other way to get out of each other's way.[6] A similar "entrapment" of flow units probably also occurs in the deformation of crystals and is at least partially responsible for the decrease in creep rate with time usually observed with such materials. It is apparent that wherever the exponential type of flow is encountered, its interpretation in terms of the simple Eyring picture should be made with some caution, since such materials may be in a torpid state in the sense outlined above.

(2) The recrystallization of cold-worked metals

We have seen that in crystalline solids such as metallic lead the inability of the elements of the crystal lattice to rearrange themselves during an experimental measurement does not seem to have any effect on the normal thermodynamic properties. But if the solid has been cold-worked this factor becomes more important, since the return of the deformed crystals to their normal equilibrium structure can occur at a finite rate only if the atoms or molecules in the lattice are sufficiently mobile. The *recrystallization temperature* of crystalline solids is thus probably analogous to the glass-transformation temperature of supercooled liquids, and its numerical value presumably depends on factors similar to those which fix T_g.

---

[6] It seems likely that such conditions, which will be expected to become more stringent with increasing chain lengths, are responsible for the Flory equation for the melt viscosity as a function of molecular weight: $\eta = \text{const.} \times \exp(b\sqrt{M})$, where b is a positive constant.

In table 3 is a comparison of the observed recrystallization temperatures with the "T_g" values estimated from self-diffusion data for various metals in the manner outlined previously in this paper (Section II,D). A rough correlation is seen to exist, but apparently the recrystallization temperature tends to be rather *lower* than the calculated T_g. Now the recrystallization process would be expected to require a great many successive jumps by the various atoms in the crystal, so that we should expect that the recrystallization temperature would be, if anything, *higher* than T_g calculated in this manner. The explanation for this discrepancy is that cold-working markedly increases diffusion rates, as has been found experimentally by Fonda, Walker, and Young (21). The diffusion data used in table 3, on the other hand, were obtained on well-annealed metals, so that we have grossly underestimated the diffusion rate, and hence the jump rate, in the cold-worked condition which characterizes metals showing recrystallization.

TABLE 3

Comparison of recrystallization temperatures of metals and T_g estimated from self-diffusion data

METAL	$\log_{10} k_0$*	TEMPERATURE FOR $k_0 = 1$ SEC.$^{-1}$	TEMPERATURE FOR $k_0 = 1$ DAY^{-1}	OBSERVED RECRYSTALLIZATION TEMPERATURE (3)	REFERENCE
		°C.	°C.	°C.	
Lead	$15.7 - 6110/T$	116	35	0	(4)
Zinc					
∥ axis	$14.7 - 4460/T$	130	-28	15	(54)
⊥ axis	$17.0 - 6800/T$	127	49		
Copper	$16.0 - 12550/T$	512	371	200	(4)
Silver	$15.0 - 10100/T$	401	272	200	(34)
Gold	$17.1 - 11200/T$	382	271	200	(4)

* k_0 = jump rate ≅ $10^{15} D$ sec.$^{-1}$, where D is the self-diffusion constant at temperature T in units of cm.^{2}/sec. (see Section II, D).

The well-known observation that recrystallization temperatures are lowered by increasing the amount of cold working is probably also due in part to this effect.

III. THE BEHAVIOR OF NON-VITREOUS LIQUIDS AT LOW TEMPERATURES

The vitreous or glassy state of liquids evidently only exists because experiments performed by mortal beings must of necessity be of limited duration. It is interesting to speculate on the behavior which liquids would show at very low temperatures if enough time could be allowed in thermodynamic measurements to avoid vitrification. Would it be found under these conditions that the non-vitreous liquid could exist in any kind of metastable equilibrium close to the absolute zero?

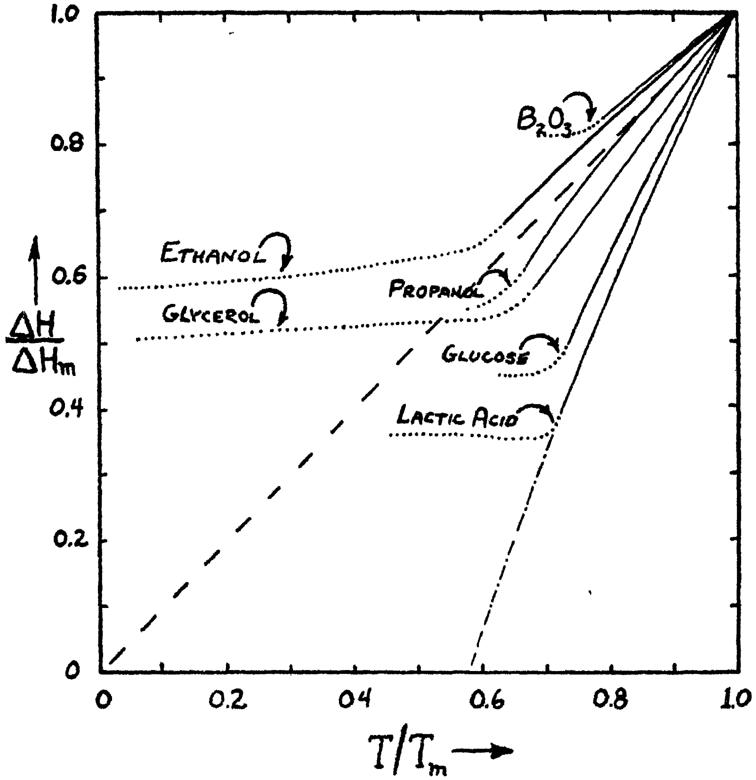


FIG. 3. Differences in heat content between the supercooled liquid and crystalline phases. Abscissa: temperature expressed as fraction of the melting temperature. Ordinate: difference in heat content expressed as fraction of the heat of fusion. ——, normal supercooled liquid; · · · , glassy state; ·—·—·—, presumed behavior of normal supercooled lactic acid below the glass-transformation temperature. See table 1 for references for data.

A. The experimental evidence

In trying to answer this question it is pertinent to compare the trends in the temperature dependence of the thermodynamic properties of crystals and their supercooled melts above the glass-transformation point. These trends can then be extrapolated to lower temperatures in order to throw some light on the above question. The available data are summarized in figures 3 to 6. Their trends are rather startling. It is seen that for glucose, for instance, the entropy of the liquid phase is rapidly approaching equality to the entropy of the crystalline phase when vitrification sets in. The heat contents of liquid and crystalline glucose seem likewise to be approaching equality at temperatures well above absolute zero. The same is true of the specific volume of liquid and crystalline glucose. Lactic acid shows the same behavior to an even more marked degree than does glucose, while glycerol, ethyl alcohol, and propyl alcohol show it to a somewhat lesser degree. Boron trioxide, on the other hand, seems not to show it at all, partly, perhaps, because it becomes a glass at a relatively higher temperature than the other substances mentioned.

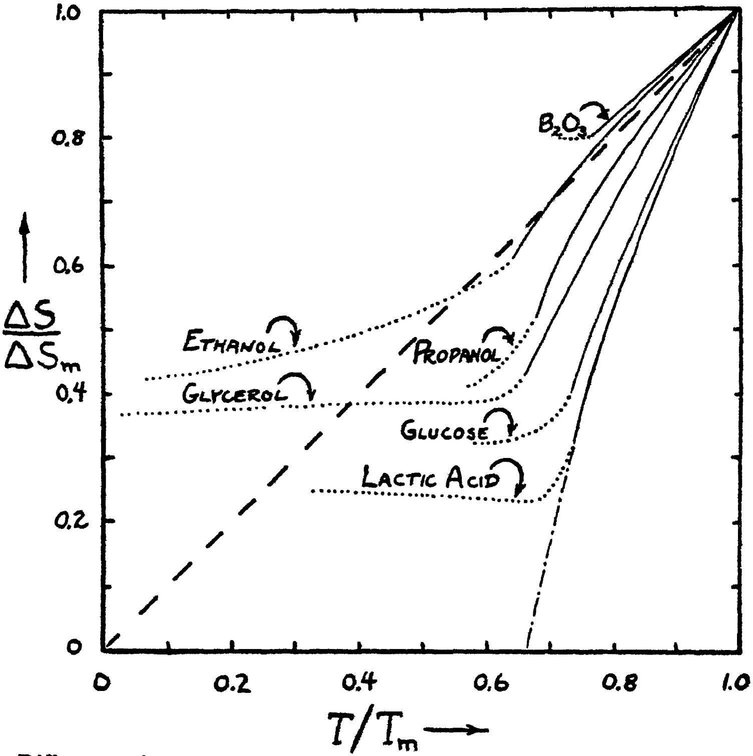


FIG. 4. Differences in entropy between the supercooled liquid and crystalline phases. Abscissa: as in figure 3. Ordinate: difference in entropy expressed as fraction of the entropy of fusion.

B. An apparent paradox

It might be argued that these results show that the non-vitreous liquid can somehow pass continuously over into the crystalline state in a manner analogous to the liquefaction of gases above the critical temperature (see, for example, Simon (85)). There is little justification for such a view, however, since the entropy curves do not seem to approach the abscissa at the same temperatures as the heat content curves. Moreover, the free energies of the two phases show no tendency to approach one another down to T_g (figure 5).

Then how are these curves to be extrapolated below T_g? Certainly it is unthinkable that the entropy of the liquid can ever be very much less than that of the solid.[7] It therefore seems obvious that the "true" or "non-vitreous" curves of $S_{\text{liq}} - S_{\text{cryst}}$ *vs.* temperature must become horizontal below some temperature not very far from T_g. Such a change in the slope of the entropy curves, however, implies a similar change in the slope of the $H_{\text{liq}} - H_{\text{cryst}}$ *vs.* temperature curves, since the two slopes are related by the expression:

---

[7] It could conceivably become slightly less at finite temperatures because of a "tighter" binding of the molecule in the highly strained liquid structure, with consequent higher frequencies of vibration and a lower density of vibrational levels.

$$\left[\frac{\partial(H_{\text{liq}} - H_{\text{cryst}})}{\partial T}\right]_p = T\left[\frac{\partial(S_{\text{liq}} - S_{\text{cryst}})}{\partial T}\right]_p$$

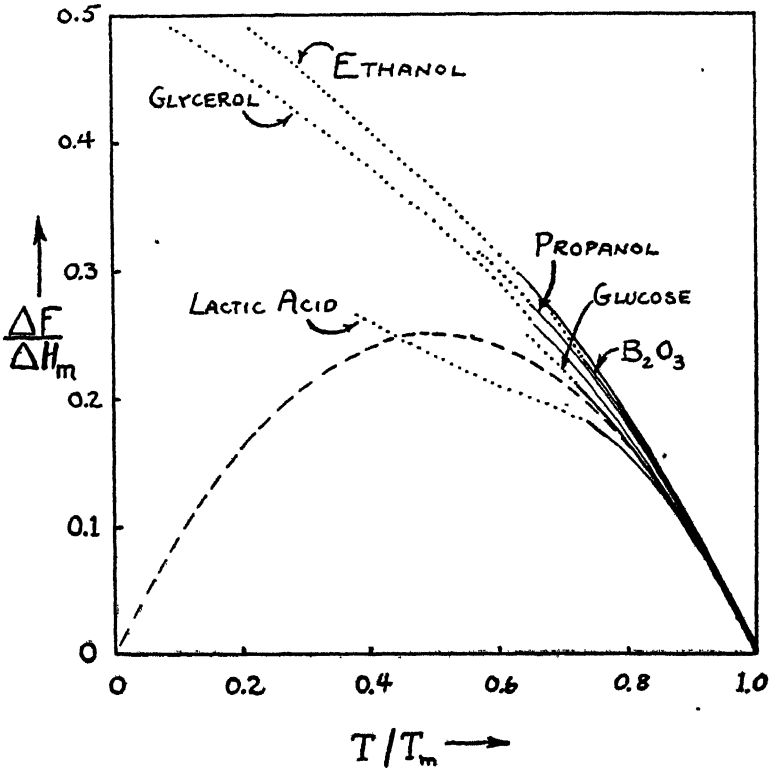


FIG. 5. Differences in free energy between the supercooled liquid and crystalline phases. Abscissa: as in figure 3. Ordinate: difference in free energy expressed as fraction of the heat of fusion.

But if $\partial(H_{\text{liq}} - H_{\text{cryst}})/\partial T$ drops to zero, then the specific heat of the liquid must of course become equal to the specific heat of the crystal. This, however, is exactly what happens in the glass transformation, which we have interpreted as a relaxation phenomenon having little to do with the "true" equilibrium thermodynamics of liquids. Is this a coincidence? Or might the glass transformation, at least in some if not all instances, really be a thermodynamic phenomenon?

C. A resolution of the paradox

Without a much more detailed experimental study of the glass transformation, particularly in glucose and lactic acid, no definite answers can be given to these questions. Perhaps in some instances a thermodynamic "freezing-in" of degrees of freedom does take place as a desperate result of the liquid's excessive generosity with its limited supply of entropy and energy as its temperature is lowered below the melting point. This would imply the existence of some kind of state of high order for the liquid at low temperature which differs from the normal crystalline state. A plausible structure for such a state seems, however, difficult to conceive, and we believe that the paradox is better resolved in another way, involving a closer inspection of exactly what one means by the metastability of liquids and glasses at low temperatures.

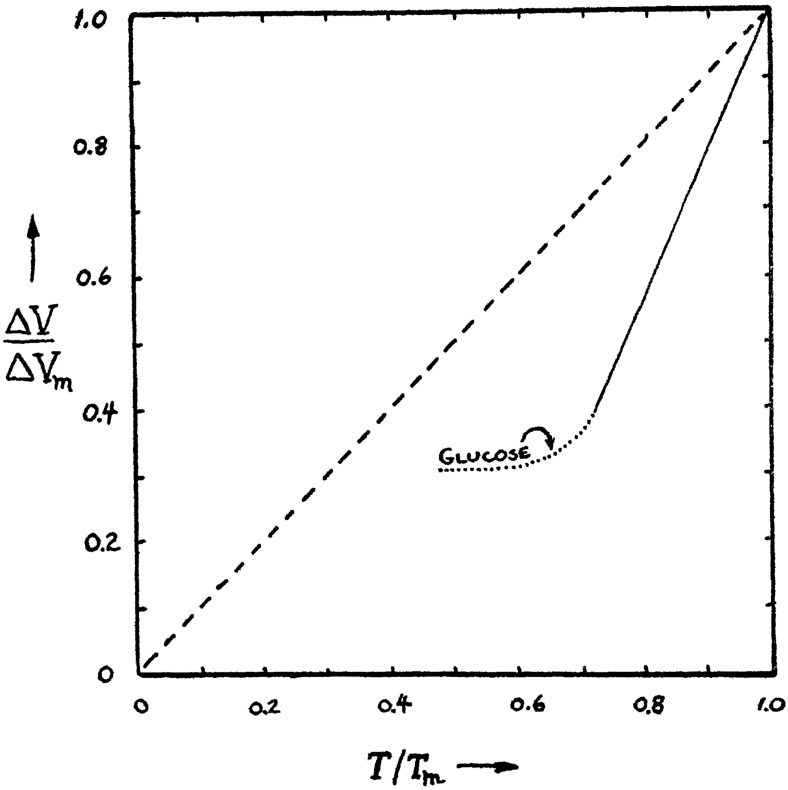


FIG. 6. Difference in specific volume between the supercooled liquid and crystalline phases of glucose. Abscissa: as in figure 3. Ordinate: difference in specific volume expressed as fraction of the change in volume on fusion.

Throughout this discussion we have been making implicit use of the idea that there are two kinds of metastability possible in liquids: *viz.*, that shown by a normal supercooled liquid with respect to the crystal, and that shown by a glass with respect to the normal supercooled liquid. Now metastability implies the existence of a free energy barrier between the metastable state and the normal state. In this case the first kind of metastability arises chiefly from the free energy barrier preventing the formation of crystal nuclei (23, 92, 102), while we have shown that the second kind of metastability is made possible by the free energy barriers which impede the motions of molecules from one equilibrium position in the liquid to another. As the temperature is decreased the height of the first kind of barrier generally decreases very markedly (see Appendix B) while the height of the second kind increases (see table 4). Suppose that when the temperature is lowered a point is eventually reached at which the free energy barrier to crystal nucleation becomes reduced to the same height as the barriers to the simpler motions. (This assumption is shown to be plausible in Appendix B and in Section III,E, below.) At such temperatures the liquid would be expected to crystallize just as rapidly as it changed its typically liquid structure to conform to a temperature or pressure change in its surroundings. It would then become operationally meaningless to speak of a metastable non-vitreous liquid as distinguished from a glass; the two kinds of metastability would merge.

Furthermore, we have mentioned in the introduction to this paper that in order for the distinction between the supercooled liquid and the crystal to have theoretical significance there must be a reasonably clear-cut boundary between the regions in phase space corresponding to the two states. If the free energy barriers between the two states become too low this boundary becomes indefinite, and it is meaningless theoretically as well as experimentally to speak of a non-vitreous liquid.

TABLE 4

Temperature dependence of the free energy of activation for dipole rotation in glycerol
($\Delta F\ddagger = RT \log kT\tau/h$, where τ is the dielectric relaxation time; see reference 36)

TEMPERATURE	LOG_{10} DIELECTRIC RELAXATION TIME*	$\Delta F\ddagger$
°K.		cal./mole
186	2.275	12,700
208	−1.477	10,700
228	−4.00	9,070
244	−5.00	8,580
266	−6.78	7,220
290	−7.99	6,250
326	−8.72	5,950

* Time in seconds. Data from references 43 and 58.

Let us denote by T_k the temperature at which the two kinds of barriers become equal. T_k may be above or below the glass-transformation point, T_g, as defined in terms of the "conventional" duration of an experiment. If T_k is *above* T_g it will be impossible for the liquid to be studied as a liquid at temperatures between T_k and T_g other than by experiments of much shorter duration than the "conventional" one, since it will crystallize spontaneously during any experiments requiring more time than the average time between simple molecular jumps. According to the concepts presented in the previous part of this paper, adequate measurements under these circumstances would result in glass-like properties for the liquid. On the other hand, if T_k is *below* T_g it is still possible to distinguish between a glassy state and a true metastable liquid between T_g and T_k.

But below T_k no such distinction is possible; the glass is then the only experimentally attainable form of the liquid as well as the only form of the liquid whose phase integral has theoretical significance. Accordingly, provided the free energy barriers vary with the temperature in the way that we have postulated, it is not permissible to extrapolate the curves in figures 3 to 6 indefinitely below T_g and to infer thereby the existence of a "thermodynamic" glass-like transition.

In the past there has been a considerable amount of speculation concerning the existence of a critical point between crystalline and liquid states analogous to the critical point between liquids and gases. No experimental evidence for or against such a critical point has ever been found (86), though there is reason to believe that none is possible (Bernal (8); but see Frenkel (22) and page 155 of reference 23). It is apparent, however, that the behavior with which we are here concerned has a certain similarity to the behavior at a critical point in that here, as at a true critical point, the free energy barrier between the crystal and the liquid disappears. On the other hand, there is a fundamental difference in that the two states do not really merge and their free energies are decidedly different (see figure 5), so that one cannot go reversibly from the one state to the other without a normal phase change. It therefore seems appropriate to refer to the temperature T_k as a "pseudocritical point." T_k might also be called a "lower metastable limit," although this term is already used in a slightly different, more operational sense (page 7 of Volmer (102)).

D. Comparison of the rates of entropy loss in hydrogen-bonded and non-hydrogen-bonded liquids

It is probably significant that all of the substances in figures 3 and 4 which show the marked tendency for the properties of the liquid and solid to approach one another are strongly hydrogen-bonded. Unfortunately similar data are not available for other types of compounds—except for boron trioxide, which, however, becomes a glass too close to its melting point to give any useful comparative information. It is interesting in this connection to compare the rates of entropy change with temperature for the crystalline and liquid forms of various types of substances near their melting points. Consider the derivative of the quantity $(\Delta S/\Delta S_m)$ with respect to T/T_m, where ΔS is the difference in entropy between the liquid and the solid at a temperature T, and ΔS_m is this difference at the melting point, T_m. If this derivative has the value unity at the melting point, then the initial part of a plot such as is given in figure 4 will fall on the 45° diagonal line of that figure. If its value is greater than unity at the melting point, a behavior similar to that of glucose or lactic acid will be found. If its value is less than unity we may expect either a behavior like that of ethyl alcohol, with a delayed downward plunge of the curve, or there may be no downward plunge at all, and hence no tendency for the entropies of the two phases to become equal above absolute zero. Now

$$\frac{\mathrm{d}\,\dfrac{\Delta S}{\Delta S_m}}{\mathrm{d}\,\dfrac{T}{T_m}} = \frac{T_m}{\Delta S_m}\frac{\mathrm{d}\Delta S}{\mathrm{d}T} = (\text{at}\quad T = T_m)\,\frac{\Delta C_{pm}}{\Delta S_m}$$

where ΔC_{pm} is the difference in the specific heats of the solid and liquid at the melting point. Values of the slopes at T_m calculated in this way for various types of materials are given in table 5. Evidently hydrogen-bonded liquids tend to lose their entropies relatively much more rapidly than other kinds of liquids, and the behavior with which we have been concerned is for most other types of substances either delayed over a considerable temperature interval below the melting point, or does not occur at all. It should be noted, though, that the specific heats of solids almost always decrease with decreasing temperature much more rapidly near the melting point than do those of liquids. If this tendency persists very far below the melting point, the entropy of the liquid must ultimately approach that of the solid very rapidly at some temperature above absolute zero.

TABLE 5

Relative rates of loss of entropy with temperature by liquids and crystals at their melting points
(Data from Landolt-Börnstein (47))

SUBSTANCE	$(\Delta C_p)_m/(\Delta S_m)$	SUBSTANCE	$(\Delta C_p)_m/(\Delta S_m)$
Mercury	0.000	Naphthalene	0.15
Bismuth	0.068	Biphenyl	0.66
Cadmium	0.080	Triphenylmethane	0.90
Copper	0.029	Pentacosane	0.37
		Tritriacontane	0.16
Nitrogen	0.71	Mannitol	1.60
Carbon monoxide	0.55	Erythritol	1.10
Nitrous oxide	0.53	Water	1.79

E. Interpretation in terms of a simple liquid model

In the above discussion we have proposed that at low temperatures the free energy barrier to the formation of a stable crystal nucleus will decrease until it becomes of the same order as the barrier for simple molecular rotation or flow. This assumption is made plausible by a consideration of a theory of the microcrystalline structure of liquids proposed by Mott and Gurney (59). Although this theory is undoubtedly rather poor in the neighborhood of the melting point, it should become increasingly satisfactory as the liquid is supercooled.

Mott and Gurney assume that a liquid is really a mass of tiny crystals more or less randomly oriented with respect to each other. Assume that the crystallites are cubes all equal in size and having sides of length a, where a is measured in units of the length of the side of a cubical unit cell. Then the surface area of each crystallite will be $6a^2$. If there are n atoms per unit cell and there are N atoms in the sample of the liquid, the total volume will be N/n times the volume of a unit cell and the total number of crystallites will be N/na^3. The total intercrystalline surface area will then be $3N/na$. If this surface has an interfacial energy of σ ergs per unit cell face, the energy of the liquid will be greater than that of the monocrystalline solid by an amount $E = 3N\sigma/na$.

Each crystallite will only be able to assume a limited number of orientations relative to its neighbors, the stable orientations being those for which its surface pattern matches the patterns of its neighbors. This matching is never perfect (whence the surface energy term), but in general we can expect that the number of stable configurations will increase with the crystallite size according to some power law: Number of configurations = Ja^m. We can expect that the exponent m in the power law will not be very different from 2, since the number of possible matchings should be roughly proportional to the number of unit cell faces on the crystallite surface. Also, when a approaches unity we can expect that the number of configurations will approach unity, so that J will be of the order of unity.

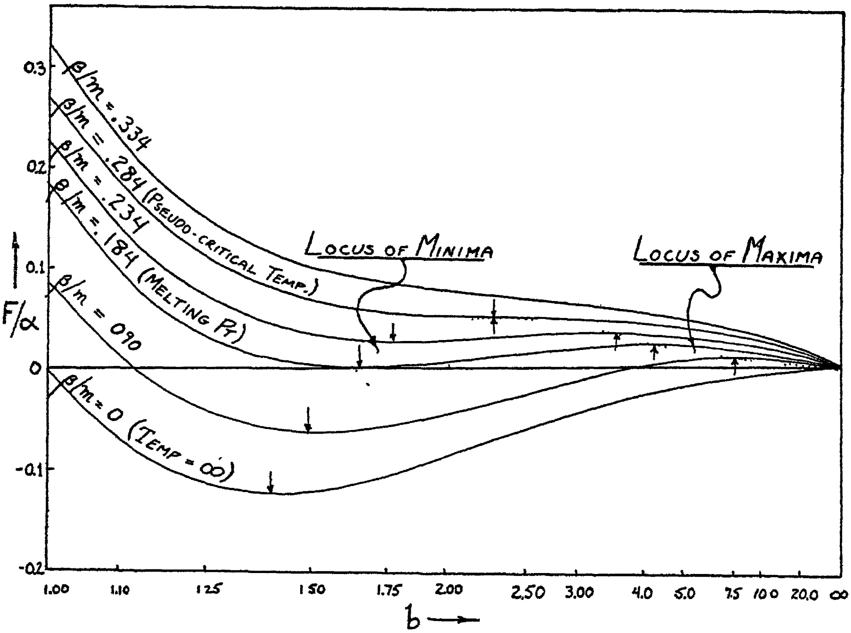


FIG. 7. Dependence of free energy of a liquid on "crystallite size" according to the Mott–Gurney theory of liquids.

The total number of configurations of the N/na^3 crystallites is $(Ja^m)^{N/na^3}$, so that the entropy is

$$S = (Nk/na^3) \log Ja^m$$

Thus we have for the difference in free energy between the liquid and the crystal

$$F = E - TS = 3N\sigma/na - (NkT/na^3) \log Ja^m$$

$$= \alpha\left[\beta/mb - \frac{\log b}{b^3}\right]$$

where $\alpha = mNJ^{3/m}kT/n$, $\beta = 3\sigma/J^{2/m}kT$, and $b = J^{1/m}a \cong a$.

In figure 7 the reduced free energy, $(1/\alpha)F$, is plotted against the reduced crystallite size, b, for various values of β/m. It is found that at infinitely high temperature ($\beta = 0$) there is a free energy minimum at $b = e^{1/3} = 1.395$, this value of b being independent of the values of m, σ, n, and J. As the temperature is decreased the value of b corresponding to the stable liquid decreases slowly until the melting point is reached. Here $F = 0$, giving $b = e^{1/2}$ and $\beta = m/2e$. At the melting point the liquid and the crystal are separated by a free energy barrier having its maximum at $b = 4.25$ and a height $0.303\Delta E_m$, where ΔE_m is the energy of melting for N atoms. As the temperature is lowered below the melting point this barrier decreases in height and occurs at smaller values of b, until at a temperature of 0.65 times the melting temperature the minimum and maximum merge and the barrier vanishes. This temperature would correspond to the "pseudocritical temperature," T_k, mentioned in the previous section. Below it the only barriers to crystallization are those which impede the growth of *stable* crystal nuclei. As Richards (75) has shown, these must be similar to those in dielectric relaxation, and by our earlier arguments these in turn are the barriers involved in glass formation.

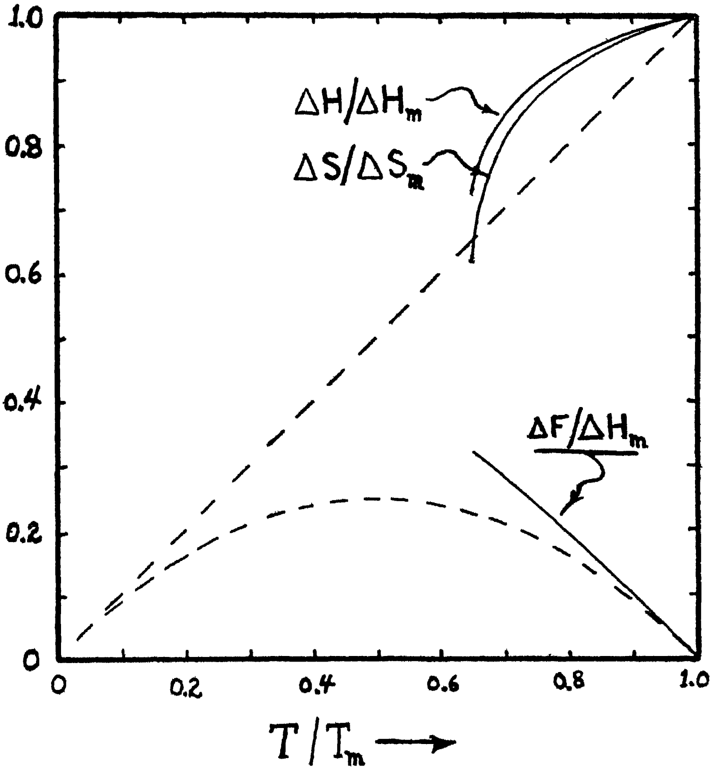


FIG. 8. Difference in the heat content, entropy, and free energy of the supercooled liquid and crystalline phases according to the Mott–Gurney theory of liquids. *Cf.* figures 3 to 5.

In figure 8 is shown the behavior of the energy, entropy, and free energy of the supercooled liquid with temperature according to this theory. The general trends are similar to those in figures 3 to 5, but the heat and entropy curves slope more gradually near the melting point. (We have seen, however, that the substances in figures 3 to 5 are generally abnormal in this respect as compared with simpler liquids.) The tendency for the energy and entropy curves in figure 8 to plunge toward the abscissa just above T_k is particularly striking.

On this crude model the entropy of melting is

$$\Delta S_m = \frac{mJ^{3/m}}{2ne^{3/2}} R = \frac{m}{9n} R \text{ per mole}$$

where R is the gas constant. Now m can hardly be much larger than 2 or 3, and for the face-centered cubic lattice $n = 4$, so ΔS_m is only $R/12$ at most. Observed entropies of melting are of the order of ten times this for such cubic crystals, however, so this model must underestimate the degree of disorder in the liquid very badly, at least in the neighborhood of the melting point.

Thus, although the quantitative aspects of the Mott–Gurney theory are rather unsatisfactory, it offers a simple and possibly essentially correct model for the interpretation of the phenomena in supercooled liquids. A theory of liquids proposed by Bresler (12) employing order–disorder theory with empty lattice sites (holes) also predicts the existence of a "pseudocritical temperature," T_k.

IV. Appendix A

Lowering of the melting point due to the finite size of a crystal

If σ is the surface free energy per unit area of the solid–liquid interface, then the free energy of a crystalline cube whose sides are of length r and whose density is ρ will be

$$\rho r^3 \mu_s = 6r^2\sigma + \rho r^3 \mu_{0s}$$

where μ_{0s} is the chemical potential of an infinitely large crystal (i.e., surface effects neglected) and μ_s is the chemical potential with the surface energy included. The chemical potential of the liquid is μ_l. At the true melting point, T_m (corresponding to $r = \infty$),

$$\mu_l(T_m) = \mu_{0s}(T_m)$$

At any other temperature, T,

$$\mu_l - \mu_{0s} \cong \left[\frac{\partial(\mu_l - \mu_{0s})}{\partial T}\right]_{T=T_m} (T - T_m) = -\frac{H}{T_m}(T - T_m)$$

where H is the heat of fusion per unit mass. The melting point of a crystal of size r will occur when $\mu_l = \mu_s$. Thus

$$T_m - T \cong 6\sigma T_m/\rho r H$$

Since σ and H are in all practical cases positive, T is always less than T_m.

The amount of the lowering of the melting point from this source is probably rather small in most cases. Taking $\sigma = 10$ ergs/cm.^{2} and $\rho H = 50$ cal./cc., one finds $(T_m - T)/T_m = 3 \times 10^{-8}/r$, so that r would have to be of the order of 1 micron to give a lowering of 0.1°C. for a substance melting at room temperature.

V. Appendix B

Evaluation of the height of the free energy barrier to crystal nucleus formation

Assume that a cube-shaped crystallite of volume V and surface area $6V^{2/3}$ is immersed in its liquid phase. Let H, S, and T_m be, respectively, the heat of fusion per cubic centimeter, the entropy of fusion per cubic centimeter, and the melting point of an infinitely large crystal ($T_m = H/S$). Let σ be the surface tension of the crystal–liquid interface. Then the free energy of the crystallite at temperature T will be

$$F = (TS - H)V + 6\sigma V^{2/3} = \frac{(T - T_m)}{T_m} HV + 6\sigma V^{2/3}$$

If $T < T_m$, this function goes through a maximum when plotted against V, the maximum being higher and at larger V, the closer T is to T_m. The maximum occurs at

$$V = \frac{64\sigma^3}{H^3}\left(\frac{T_m}{T_m - T}\right)^3$$

giving for the free energy at the top of the barrier:

$$F_{\max} = \frac{32\sigma^3}{H^2}\left(\frac{T_m}{T_m - T}\right)^2$$

Thus the barrier height decreases inversely as the square of the degree of supercooling.

Taking $\sigma = 10$ ergs/cm.^{2} and $H = 50$ cal./cc. as reasonable values, we find

$$\begin{aligned} F_{\max} &= 8 \times 10^{-15}(T_m/T_m - T)^2 \text{ ergs per crystal} \\ &= 120(T_m/T_m - T)^2 \text{ calories per mole} \end{aligned}$$

If $T = 0.75T_m$, this gives $F_m =$ only 1900 cal./mole, which is already much less than the usual free energies of activation for molecular motions in liquids (e.g., *ca.* 10,000 cal./mole for glycerol dipole rotation; see table 4). At this temperature, however, the crystal would only measure

$$V^{1/3} = \frac{4\sigma}{H}\frac{T_m}{T_m - T} = 2 \times 10^{-8}(T_m/T_m - T) \text{ cm.} = 8 \text{ Å}.$$

so the above relation for F_m is undoubtedly a rather crude approximation this far away from the melting point.

VI. References

(1) Alexandrov, A. P., and Lazurkin, I. S.: Acta Physicochim. U.R.S.S. **12**, 647 (1940).
(2) Alfrey, T. A., Goldfinger, G., and Mark, H.: J. Applied Phys. **14**, 700 (1943).
(3) Archer, R. S.: *American Society for Metals Handbook*, p. 198 (1939).

(4) Barrer, R. M.: *Diffusion in and through Solids*, p. 275. The Macmillan Company, New York (1941).
(5) Bekkedahl, N.: J. Research Natl. Bur. Standards **13**, 411 (1934).
(6) Bekkedahl, N., and Matheson, H.: J. Research Natl. Bur. Standards **15**, 503 (1935).
(7) Bekkedahl, N., and Scott, R. B.: J. Research Natl. Bur. Standards **29**, 87 (1942).
(8) Bernal, J. D.: Trans. Faraday Soc. **33**, 27 (1937).
(8a) Bernal, J. D., and Fowler, R. H.· J. Chem. Phys. **1**, 518 (1933).
(9) Born, M., and Mayer, M. G.: *Handbuch der Physik*, Vol. XXIV-2, p. 698ff.
(10) Boyer, R. F., and Spencer, R. S.: J. Applied Phys. **16**, 594 (1945).
(11) Boyer, R. F., and Spencer, R. S.: Advances in Colloid Sci. **2**, 1 (1926).
(12) Bressler, S.: Acta Physicochim. U.R.S.S. **10**, 491 (1939).
(13) Clark, G. L.: *Applied X-Rays*, 3rd edition, p. 482. The McGraw-Hill Book Company, Inc., New York (1940).
(14) Clash, R., and Runkiewicz, L.: Ind. Eng. Chem. **36**, 279 (1944).
(15) Danforth, W.: Phys. Rev. **38**, 1224 (1931).
(16) Dushman, S., Dunbar, L. W., and Huthsteiner, H.: J. Applied Phys. **15**, 108 (1944).
(17) Einstein, A.: Ann. Physik **19**, 371 (1906).
(18) Eyring, H.: J. Chem. Phys. **4**, 283 (1936).
(19) Ferry, J. D., and Parks, G. S.: J. Chem. Phys. **4**, 70 (1936).
(19a) Ferry, J. D., and Parks, G. S.: Physics **6**, 360 (1935).
(20) Flory, P. J.: J. Am. Chem. Soc. **62**, 1057 (1940).
(21) Fonda, G. R., Young, A. H., and Walker, A.: Physics **4**, 1 (1933).
(22) Frenkel, J.: Trans. Faraday Soc. **33**, 58 (1937).
(23) Frenkel, J.: *Kinetic Theory of Liquids*. University Press, Oxford (1946).
(24) Fuoss, R. M., and Kirkwood, J. G.: J. Am. Chem. Soc. **63**, 385 (1941).
(25) Gee, G.: Quarterly Reviews **1**, 271 (1947).
(26) Giauque, W. F., and Stout, W.: J. Am. Chem. Soc. **58**, 1144 (1936).
(27) Gibson, G. E., and Giauque, W. F.: J. Am. Chem. Soc. **45**, 93 (1923).
(28) Greene, E. S., and Parks, G. S.: J. Chem. Phys. **9**, 262 (1941).
(29) Halsey, G.: J. Applied Phys. **18**, 1072 (1947).
(30) Halsey, G., White, H., and Eyring, H.: Textile Research J. **15**, 295 (1945).
(31) Huffman, H., Parks, G. S., and Thomas, S. B.: J. Am. Chem. Soc. **52**, 3241 (1930).
(32) Jenckel, E.: Z. anorg. allgem. Chem. **216**, 367 (1934).
(33) Jenckel, E.: Z. Elektrochem. **43**, 796 (1937).
(34) Johnson, W. A.: Metals Technol. **8**, Paper No. 1272 (1941).
(35) Kauzmann, W.: Metals Technol. **8**, Paper No. 1301 (1941); Trans. Am. Inst. Mining Met. Engrs., Inst. Metals Div. **143**, 57 (1941).
(36) Kauzmann, W.: Rev. Modern Phys. **14**, 12 (1942).
(37) Kauzmann, W., and Eyring, H.: J. Am. Chem. Soc. **62**, 3113 (1940).
(38) Keesom, W.: *Helium*, p. 256. Elsevier Publishing Company, Amsterdam (1942).
(39) Kelley, K.: J. Am. Chem. Soc. **51**, 779 (1929).
(40) Kelley, K.: J. Am. Chem. Soc. **51**, 1400 (1929).
(41) Kimura, S., and Namikawa, N.: J. Soc. Chem. Ind. Japan **32**, suppl. binding 196–7 (1929). See Bekkedahl's curve for T_g *vs.* sulfur content, Figure 3 of reference 11.
(42) Kobeko, P., Kuvshinski, E., and Gurevich, G.: J. Tech. Phys. (U.S.S.R.) **4**, 622 (1938).
(43) Kobeko, P., Kuvshinski, E., and Shushkin, N.: J. Tech. Phys. (U.S.S.R.) **8**, 715 (1938).
(44) Kobeko, P., and Shushkin, N.: J. Tech. Phys. (U.S.S.R.) **17**, 26 (1947); reported in Chem. Abstracts **41**, 5354 (1947).
(45) Kuhn, W.: Z. physik. Chem. **B42**, 1 (1939).
(46) Kuvshinski, E.: J. Tech. Phys. (U.S.S.R.) **5**, 491 (1938).
(47) Landolt-Börnstein: *Physikalisch-Chemische Tabellen*. J. Springer, Berlin.

(48) Lillie, H. R.: J. Am. Ceram. Soc. **16**, 619 (1933).
(49) Lillie, H. R.: J. Am. Ceram. Soc. **19**, 45 (1936).
(50) Littleton, J. T.: Ind. Eng. Chem. **25**, 748 (1933).
(51) Mason, W. P.: Trans. Am. Soc. Mech. Engrs. **69**, 359 (1947).
(52) Mayer, J. E., and Mayer, M. G.: *Statistical Mechanics*, p. 228. John Wiley and Sons, Inc., New York (1940).
(53) Meyer, K. H., and Ferri, C.: Helv. Chim. Acta **18**, 570 (1935).
(54) Miller, P. H., and Banks, F. R.: Phys. Rev. **61**, 648 (1941).
(55) Mondain-Monval, P.: Ann. chim. **3**, 5 (1935).
(56) Morey, G. W.: *The Properties of Glass*, p. 524. Reinhold Publishing Corporation, New York (1938).
(57) Morgan, J., and Warren, B. E.: J. Chem. Phys. **6**, 666 (1938).
(58) Morgan, S. O., and Yager, W. A.: Ind. Eng. Chem. **32**, 1522 (1940).
(59) Mott, N., and Gurney, R.: Trans. Faraday Soc. **35**, 364 (1939).
(60) Murphy, E. J.: Trans. Am. Electrochem. Soc. **65**, 133 (1934).
(61) Nelson, E. W., and Newton, R. F.: J. Am. Chem. Soc. **63**, 2178 (1941).
(62) Ostwald, W.: *Lehrbuch der allgemeinen Chemie*, Vol. II/1, p. 514. W. Engelmann, Leipzig (1910).
(63) Parks, G. S.: J. Am. Chem. Soc. **47**, 341 (1925).
(64) Parks, G. S., and Gilkey, W. A.: J. Phys. Chem. **33**, 1428 (1929).
(65) Parks, G. S., and Huffman, H.: J. Am. Chem. Soc. **48**, 2788 (1926).
(66) Parks, G. S., and Huffman, H.: J. Phys. Chem. **31**, 1842 (1927).
(67) Parks, G. S., Huffman, H., and Cattoir, F. R.: J. Phys. Chem. **32**, 1336 (1928).
(68) Parks, G. S., and Reagh, J. D.: J. Chem. Phys. **5**, 364 (1937).
(69) Parks, G. S., and Thomas, S. B.: J. Am. Chem. Soc. **56**, 1423 (1934).
(70) Parks, G. S., Thomas, S. B., and Light, D.: J. Chem. Phys. **4**, 66 (1936).
(71) Patnode, W., and Scheiber, W.: J. Am. Chem. Soc. **61**, 3449 (1939).
(72) Pauling, L.: Phys. Rev. **36**, 430 (1930).
(73) Prins, J. A., and Peterson, H.: Physica **3**, 147 (1936).
(74) Randall, J. T.: *Diffraction of X-Rays and Electrons by Amorphous Solids, Liquids and Gases*, p. 173. John Wiley and Sons, Inc., New York (1934).
(75) Richards, W. T.: J. Chem. Phys. **6**, 449 (1936).
(76) Roseveare, W. E., Powell, R. E., and Eyring, H.: J. Applied Phys. **12**, 669 (1941).
(77) Ruhemann, M., and Simon, F.: Z. physik. Chem. **A138**, 1 (1928).
(78) Samsoen, M.: Compt. rend. **182**, 517 (1926).
(79) Samsoen, M.: Ann. phys. **9**, 35 (1928).
(80) Schallamach, A.: Proc. Phys. Soc. (London) **53**, 214 (1941); Rubber Chem. and Technol. **15**, 142 (1942).
(81) Scott, A. H.: J. Research Natl. Bur. Standards **14**, 99 (1935).
(82) Seitz, F.: *Modern Theory of Solids*, p. 494. The McGraw-Hill Book Company, Inc., New York (1940).
(83) Simha, R.: Ann. N. Y. Acad. Sci. **44**, 297 (1943).
(84) Simon, F.: Ann. Physik **68**, 278 (1922).
(85) Simon, F.: Z. allgem. anorg. Chem. **203**, 219 (1931).
(86) Simon, F.: Trans. Faraday Soc. **33**, 65 (1937).
(87) Southard, J. C.: J. Am. Chem. Soc. **63**, 3147 (1941).
(88) Spaght, M. E., and Parks, G. S.: J. Phys. Chem. **38**, 103 (1934).
(89) Spencer, R. S., and Boyer, R. F.: J. Applied Phys. **15**, 398 (1944).
(90) Spencer, R. S,, and Boyer, R. F.: J. Applied Phys. **17**, 398 (1946).
(91) Stott, V. H., Irwin, E., and Turner, D.: Proc. Roy. Soc. (London) **A108**, 154 (1925)
(92) Tammann, G.: *Kristillisieren und Schmelzen*. J. Barth, Leipzig (1903).
(93) Tammann, G.: *Der Glaszustand*. L. Voss, Leipzig (1933).
(94) Tammann, G., and Gronau, H.: Z. anorg. allgem. Chem. **192**, 193 (1930).

(95) Tammann, G., and Hesse, W.: Z. anorg. allgem. Chem. **156**, 256 (1926).
(96) Tammann, G., and Jellinghaus, W.: Ann. Physik **2**, 264 (1929).
(97) Tammann, G., and Jenckel, E.: Z. anorg. allgem. Chem. **184**, 416 (1929).
(98) Tammann, G., and Kohlhaus, A.: Z. anorg. allgem. Chem. **182**, 66 (1929).
(99) Taylor, N.: J. Phys. Chem. **47**, 247 (1943).
(100) Thomas, S. B., and Parks, G. S.: J. Phys. Chem. **35**, 2091 (1931).
(101) Ueberreitter, K.: Z. physik. Chem. **B45**, 361 (1940).
(102) Volmer, M.: *Kinetic der Phasenbildung.* T. Steinkopff, Leipzig (1939).
(103) Wietzel, R.: Z. anorg. allgem. Chem. **116**, 81 (1921).
(104) Wood, L. W., Bekkedahl, N., and Peters, C. G.: J. Research Natl. Bur. Standards **23**, 571 (1939).

LIQUID-PHASE ALKYLATION OF AROMATIC HYDROCARBONS[1]

ALFRED W. FRANCIS

Research and Development Department, Socony-Vacuum Laboratories, Paulsboro, New Jersey

Received February 17, 1948

Results of the liquid-phase alkylation of aromatic hydrocarbons are affected profoundly by solvent extraction of the early reaction products in the catalyst layer. This accounts for some anomalous observations, such as premature formation of polyalkylbenzenes. Appropriate adjustments of physical conditions greatly increase the yields of monoalkylbenzenes. The alkylation is extremely rapid, perhaps even instantaneous; but delays are usually inherent in providing adequate contact among the two reagents and catalyst.

The alkylation reactions are not reversible because the equilibria are too far on the side of alkylation at moderate temperatures.

Alkyl groups have a negligible effect upon the rate of further alkylation. Their orienting effect can be considered "normal" (ortho and para directing), but it is so weak that, in view of the lability of the groups, it is readily superseded by the effect of thermodynamic stability, which may involve also steric effects. Meta isomers are formed probably by isomerization rather than dealkylation. Variations in the distribution of products with different catalysts are reconciled.

Friedel and Crafts announced their discovery of the alkylation of aromatic hydrocarbons in the liquid phase with aluminum chloride as catalyst seventy years ago (23). Innumerable investigations of this reaction have been made since that time. The process is extremely flexible, so that a wide variety of catalysts and alkylating agents is available under appropriate conditions, with corresponding variation in distribution of products. Results have already been reviewed so thoroughly by Calloway (16), Nightingale (46), Price (56, 57), and Thomas (73) that a comprehensive review is not now necessary. Yields of ethylbenzene have been summarized recently (22). This paper will consider only certain aspects not usually emphasized.

Variables in conditions are the identity and the amount of the aromatic hydrocarbon, alkylating agent, catalyst, and promoter; also temperature, time, pressure, degree of stirring, and manner of introduction of reagents. The products are distributed according to the relative amounts of mono-, di-, and poly-alkyl derivatives, unchanged and isomerized alkyl groups, and position isomers of di- and poly-alkyl derivatives.

It has been difficult to correlate the results with the conditions in all cases, partly because some of the analyses, which are difficult, may not be reliable (66), and partly because of the profound effect of some physical factors in the conditions, which are not entirely predictable.

An example of the latter is the selective solvent extraction of the hydrocarbon layer by the catalyst layer. This may result in a very considerable segregation of the early reaction products, so that subsequent reaction may depend as much on such physical effects as it does on chemical reactivity. Whether this factor is favorable or not depends upon the object of the reaction and on the manner of applying the alkylating agent, but it should not be neglected.

---

[1] Presented at the symposium on "Mechanism of Hydrocarbon Reactions" of Section C of the American Association for the Advancement of Science at its 114th Meeting, Chicago, Illinois, December 27, 1947. Portions of the paper were presented also at the Meeting-in-Miniature of the Philadelphia Section of the American Chemical Society, January 22, 1948.

This factor is especially pertinent to the distribution of products between mono- and poly-ethylbenzenes. Usually the monoethylbenzene is desired because of its importance in making styrene, etc. The aim of a high yield of monoethylbenzene has resulted in many patents (*cf.* 22 for list) covering the use of a large excess of benzene over ethylene, or the idea of recycling the polyethylbenzenes, since it is possible to transfer some of the excess ethyl groups to another benzene molecule. But the recycling of either the benzene or the polyethylbenzenes involves additional expense in distillation, catalyst consumption, and effective capacity of equipment, so that it should be minimized.

The opinion has been general (9, 35, 45, 46, 57, 73) that benzene is less reactive in alkylation reactions than its alkyl derivatives, and this supposition has been blamed (57) for the accumulation of polyethylbenzenes. It is evident, however, that if the heavy catalyst layer has a selective solvent action, dissolving more ethylbenzene than benzene as has been shown (9, 39), and that if the only reaction takes place in that layer, a similar accumulation of polyalkylbenzenes would result.

This unfavorable consequence might be avoided either by eliminating the selective solvent action, or by changing conditions so that alkylation takes place in the hydrocarbon layer. Both have been tried with good results. The selective solvent effect was eliminated (22) by the use of a mutual solvent, ethyl ether, which rendered the reaction mixture homogeneous. The distribution of products corresponded exactly to that calculated on the assumption that the rate of ethylation of benzene is the same as that of each of its ethyl derivatives (except hexaethylbenzene). Other means of eliminating the unfavorable selection are high-speed stirring (9, 39, 42) and vapor-phase operation (at least twenty-five citations; for example, 52), which gave similar results.

The hydrocarbon layer was rendered catalytic for the ethylation by using a higher temperature, 100°C. (22), at which the solubility of aluminum chloride in benzene is sufficient. The selective solvent action of the catalyst layer then gave a favorable result. The ethylbenzene formed in the early part of the reaction was partly extracted and protected from further attack of the ethylene, which was applied under pressure from the vapor phase and never came into direct contact with the catalyst layer. These various modes of operation are illustrated in figure 1.

The above physical mechanism would account in considerable degree for many observations in the literature concerning low-temperature alkylation. Because of the low solubility of aluminum chloride in benzene (*cf.* 73, page 461) the only reaction at first is at the surface of the solid catalyst. This is the "incubation period" commonly observed (9, 39, 42, 73, 74). After some ethylated benzene is formed, a liquid complex with the catalyst results, giving a renewable surface of contact, which allows more rapid reaction. Still the only reaction is in the catalyst layer, which contains a relatively small amount of aromatic hydrocarbon. As ethylene is added, it gives effectively a large excess in the catalyst phase and readily forms hexaethylbenzene there, even with a mole fraction of much less than 1 mole of ethylene to 1 mole of total benzene (9, 21, 39, 42).

With more time the highly ethylated products are gradually reëxtracted by the benzene layer and partly deëthylated. This redistribution is facilitated by larger amounts of catalyst, by high-speed stirring, and by higher temperature (39, 42).

The view that the formation of hexaethylbenzene is the result of physical selection rather than of chemical mechanism is supported by the observation that none of it was found in any product made under conditions where the hydrocarbon layer was catalytically active and where the ethylene was added from the vapor phase (22). The homogeneous alkylation reaction is so rapid, however, that if ethylene is bubbled through the catalytic hydrocarbon layer, a little hexaethylbenzene is formed as a result of local excesses (22).

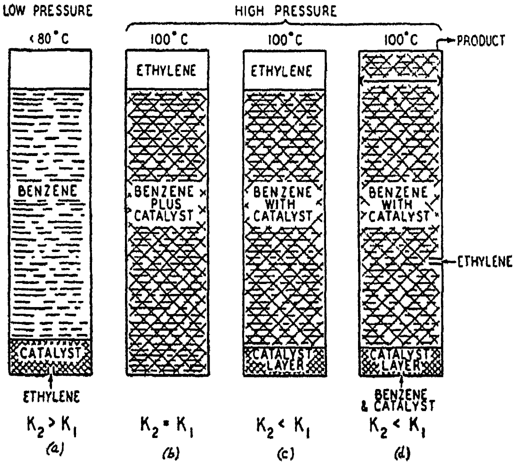


FIG. 1. Diagrammatic conditions for ethylation of benzene (22): (a) laboratory low-temperature operation; (b) homogeneous (solventized) liquid-phase ethylation; (c) ethylation with pressure and higher temperature (no homogenizing solvent); (d) semicontinuous operation. Crosshatching indicates catalyst dissolved in sufficient quantity for catalytic action. (Courtesy of *Industrial and Engineering Chemistry*.)

The "instantaneous" character of the real chemical reaction, thus demonstrated, seems in marked contrast to the long time commonly provided for the ethylation of benzene, usually 2–5 hr. (nineteen citations; for example, 3) or even more (fourteen citations; for example, 45). Speeding of the reaction requires adequate contact between the reagents and catalyst, which apparently can be attained only by solution of catalyst in the benzene. Even the 3-min. reaction time reached in one experiment (22) was probably slow compared with the chemical reaction, and like all ethylations was probably a measure of the rate of introduction of the ethylating agent into the system.

Factors which probably influenced this rate were the much larger volume in which the reaction was taking place, the much higher pressure of ethylene (100–300 lb. instead of only a few millimeters partial pressure when ethylene is bubbled through benzene at atmospheric pressure near the boiling point), and the retention of hydrogen chloride at pressures up to about half an atmosphere instead of allowing it to escape with unreacted hydrocarbon gases. The promoting effect of the hydrogen chloride upon aluminum chloride is well known qualitatively, but nothing seems to have been published on a relation between its partial pressure and its promoting effect. Thomas (73, page 79) even indicated that it should be withdrawn to avoid reversing the reaction with ethyl halide.

REVERSIBILITY

It has often been stated that Friedel–Crafts alkylations are reversible (12, 16, 36, 38, 43, 46, 56, 57, 73). It is true that alkyl groups above methyl are readily transferred from one position to another in the same ring, and from one benzene nucleus to another, so that polyethylbenzenes react with benzene to give ethylbenzene. Isopropyl and *tert*-butyl groups are still more readily transferred, and one alkyl group can displace another (11, 15). Similarly, stirring pure ethylbenzene with aluminum chloride at room temperature for a few minutes gave substantial amounts of benzene and polyethylbenzenes (4, 22).

The methyl group is much more refractory in these rearrangements, so that toluene on long-time boiling under reflux with aluminum chloride gives little benzene and xylene (21), or is formed from them (12). Yet even methyl groups have been transferred in liquid-phase reactions (4, 5, 29, 36, 44, 46). Ethylation of toluene under vigorous conditions has given hexaethylbenzene (21). The byproduct, not isolated, might be an ethylated xylene.

True reversibility implies the dissociation of alkylbenzene into benzene and olefin, or the regeneration of some other ethylating agent. This does not take place with aluminum chloride or other catalysts at reaction temperatures for liquid-phase alkylation. Although benzene was distilled off rapidly from ethylbenzene heated under a column with aluminum chloride, no uncondensed gas (ethylene) appeared, and the residue was highly ethylated (22). Ethyl groups were shifted, but there was no reversal of ethylation.

The reason is that the thermodynamic equilibrium is so far on the side of alkylation at moderate temperatures that the partial pressure of ethylene is negligible. This is shown in table 1, calculated from equilibrium constants selected by the Bureau of Standards (2). The equilibrium is represented approximately by the equation $\log K = 5460/T - 6.56$.

Even at 300°C. hexaethylbenzene with zinc chloride or 97 per cent phosphoric acid failed to evolve appreciable amounts of ethylene (21). At the higher temperature of some vapor-phase processes there is a true equilibrium. Most of these processes operate at 300–500°C., at which the equilibrium is still favorable for alkylation. Transfer of alkyl groups at 454–538°C. was studied by Hansford, Myers, and Sachanen (28), and showed only a slight production of olefins in this temperature range. One patent (40) gives data from which can be calculated K = about 12 at 550–600°C., a value which is slightly higher than would be expected from the Bureau of Standards data (2). If this calculation is valid, it means a still lower equilibrium partial pressure of ethylene in table 1 in the high-temperature range.

The equilibrium between cumene, benzene, and propylene is not much more favorable to decomposition, the calculated partial pressure of propylene at 27°C. being only 10^{-3} mm. Diisopropyltoluene on heating at its boiling point (225°C.) with sodium aluminum chloride evolved no appreciable amount of propylene (21). A little gas which was produced proved to be propane (*cf.* 29, 32, 61). However, Schultze produced propylene and butenes by the decomposition of dialkylbenzenes at 400°C. or higher (62).

TABLE 1

Equilibrium constants

$C_6H_6 + C_2H_4 \rightleftharpoons C_6H_5C_2H_5$

TEMPERATURE	LOG K	PARTIAL PRESSURE OF ETHYLENE
°C.		*mm.*
27	11.6605	10^{-4}
127	7.0710	0.2
227	4.3417	5
327	2.5261	40
427	1.2382	145
527	0.2806	280

Alkylation with ethanol is calculated by combining the equation for the hydration of ethylene (from data of Aston (6))

$$\log K = 2400/T - 6.8$$

with the above equation for alkylation with ethylene, giving

$$\log K = 3060/T + 0.24$$

for $C_6H_6 + C_2H_5OH \rightleftharpoons C_6H_5C_2H_5 + H_2O$. Reversal would be negligible at all temperatures.

Alkylation with ethyl chloride is calculated by combining the equation for its dissociation (from the experimental data of Rudkovskiĭ and coworkers (60) and of Tilman (75)),

$$\log K = -3334/T + 5.75$$

with that for alkylation with ethylene, giving

$$\log K = 2126/T - 0.81$$

for $C_6H_6 + C_2H_5Cl \rightleftharpoons C_6H_5C_2H_5 + HCl$. The maximum equilibrium partial pressure of ethyl chloride below the boiling point of ethylbenzene would be about 2 mm. Jacobsen (36) claimed to have reversed the corresponding methylation by evolving methyl chloride very slowly from *m*-xylene or more highly methylated benzenes with aluminum chloride at reflux temperatures, using a stream of dry hydrogen chloride. However, the high yields of higher alkylbenzenes obtained by Simons and Hart (65) with alkyl chlorides and hydrogen chloride under high pressure and moderately high temperature proves that the equilibrium is almost entirely on the side of alkylation, with alkyl halides. The same conclusion applies to methylation with dimethyl ether (26), and to alkylation with esters.

At moderate temperatures, although the alkylations might be considered reversible kinetically, they are scarcely more reversible thermodynamically than is the formation of water from hydrogen and oxygen.

ISOMERIZED ALKYL GROUPS

This subject has been discussed extensively (16, 18, 24, 33, 34, 56, 57, 73). However, neglect of the possibility of isomerization of the alkyl group has resulted in much misidentification of alkylbenzenes in the early literature and quoted recently (*cf.* 20 for about sixteen illustrations). In the products of Friedel–Crafts reactions the resulting alkyl groups above ethyl are rarely primary except from cycloparaffins (27, 34, 64) and primary alcohols (34), and under mild conditions from primary esters or halides (13, 34), especially with a long chain (25). They are usually secondary from straight-chain olefins and other reagents, and tertiary from reactants having a branch adjacent to the functional group. The phenyl group frequently assumes a position different from that occupied by the functional group of the reagent (31, 76).

On alkylation with aluminum chloride and secondary alcohols the position of the phenyl group usually can be predicted by postulating preliminary decomposition of the alcohol to olefin, followed by addition of the aromatic to one side of the double bond according to Markovnikov's rule (*cf.* 31, 78). With sulfuric acid the double bond may shift before alkylation (33, 34). This would be required in order to produce *tert*-amyl derivatives from isoamyl reagents.

Intermediate formation of olefins is not the only mechanism, however, since it is inapplicable to alkylation with methyl and benzyl (13) and neopentyl radicals (34, 54). Moreover, Price and Lund (59), Burwell and Archer (14), and Tsukervanik (76) have shown that some optical activity in the alkylating agent may be retained in the alkylbenzene.

As noted by Ipatieff, Pines, and Schmerling (34) the carbon skeleton is rarely isomerized in alkylating aromatic hydrocarbons, as stated by Calloway (16) and by Linstead (38), except with neopentyl derivatives (54). However, under vigorous isomerization a *sec*-butyl group has been rearranged to a tertiary structure (47). Moreover, Legge (37) has identified products with isopropyl and *tert*-amyl groups on per-alkylation with isobutene.

ORIENTATION IN ALKYLATION

Since alkyl groups are uniformly ortho and para directing in nitration, halogenation, and sulfonation reactions, it is usual to consider *p*-dialkylbenzenes as the "normal" products and *m*-dialkylbenzenes as "abnormal" (56, 57). The ortho isomer is not usually considered an important product except in methylation (35, 50), although recent observations on distribution for the cymenes (66) show 31–38 per cent of the ortho isomer. Sometimes the para isomer is the main product, especially with phosphoric acid (76), sulfuric acid (77), and boron fluoride (67, 78), but just as frequently, especially with a vigorous catalyst like aluminum chloride, the meta isomer is the predominant product (table 2).

Similarly, the trialkylbenzenes formed by alkylation are commonly the 1,2,4-derivatives when mild conditions are used (67), and the 1,3,5-isomers with a vigorous catalyst (50, 61, 70), but apparently no vicinal trialkylbenzene (1,2,3-) has ever been positively identified in the products of a Friedel–Crafts alkylation. This may be the result of steric influences.

It is usual to account for meta derivatives by postulating the preliminary formation of the 1,2,4-trialkyl derivative, followed by dealkylation of the group in the 1-position (5, 36, 43, 56, 57, 58). The reason for selective removal of the 1-alkyl group (58)—namely, that it is ortho to one alkyl group and para to the other—may be open to some question. The 1-alkyl group is in a preferred position for stability. In analogous cases it has been shown by Holleman and others (*cf.* 19) that the most labile substituent is the one "most out of place with respect to the directive influence of the other substituents". In the table given in reference 19 (page 259) opposite trichlorobenzenes, in the 1,2,4-isomer, the 2 should have been printed in bold type, signifying the one displaced (30).

Meta isomers might arise also by direct isomerization of para isomers, since this reaction has been accomplished (7, 29, 44, 51). Symmetrical trialkylbenzenes have been considered to result either from the dealkylation of first-formed hexaalkylbenzenes (39), or the isomerization of the 1,2,4-isomer (7, 39, 47, 61, 72), which has been accomplished.

If an isomerization occurs, giving more than 50 per cent of an isomer, it is evident that that one is the most stable thermodynamically and has the lowest free energy under the conditions of the experiment. Probably the distribution of products on isomerization is near to thermodynamic equilibrium. The same distribution is probable among isomers from alkylation under vigorous conditions (e.g., with aluminum chloride). This would be a necessary consequence if alkylation were considered reversible kinetically (even though it is not so thermodynamically); that is, that the products are sufficiently interactive.

This hypothesis can be tested for the xylenes by direct comparison with the equilibrium percentages of isomers, which were investigated by Pitzer and Scott (55), showing 12 per cent *o*-, 71 per cent *m*-, and 17 per cent *p*-xylenes, almost independent of temperature. It is quite likely that the equilibrium percentage of the ortho isomer is less for higher alkyl derivatives because of greater steric hindrance. In fact, such a difference is indicated in thermodynamic data on methylethylbenzenes from the Bureau of Standards (2).

Table 2 summarizes the isomer distribution of products in several investigations of the alkylation of benzene and alkylbenzenes in the liquid phase; and table 3 shows some isomerization studies. These tables are by no means complete (*cf.* the lists in references 57, 73) but include those with more quantitative

TABLE 2

Orientation in alkylation

REAGENTS		TEMPERATURE	PRODUCTS*			REFERENCES
Aromatic	Aliphatic		Ortho	Meta	Para	
(a) Catalyst: aluminum chloride						
		°C.				
Benzene	CH_3Cl			95	5 xylenes	(1)
Toluene	CH_3Br	−3	44.5	28	27.5 xylenes	(50)
Toluene	CH_3Br	94	8	83	9 xylenes	(50)
Toluene	CH_3Cl	0	53.5	27.3	19.2 xylenes	(50)
Toluene	CH_3Cl	55	12.2	87.1	0.7 xylenes	(50)
Toluene	CH_3Cl	106	1.8	98.2	0 xylenes	(50)
m-Xylene	CH_3Cl	100	87 Mesitylene			(50)
Xylene (technical)	CH_3Cl	130 to 140	60 1,2,3,5-} Tetramethylbenzenes 40 1,2,4,5-} Tetramethylbenzenes			(68)
Benzene	CH_3Cl	−40 to 0	Pseudocumene			(50)
m-Xylene	C_2H_5Br	−10 to 0	1,3-Dimethyl-5-ethylbenzene			(50)
Toluene	C_2H_5Br	−12 to −8	1-Methyl-3,5-diethylbenzene			(50)
Benzene	C_2H_5Br	−50 to 0	1,3,5-Triethylbenzene			(50)
Benzene	C_2H_5Cl	70 to 75	86 1,3,5-Triethylbenzene 14 1,2,4-Triethylbenzene			(70)
Benzene	C_2H_5Cl	70	50 1,2,3,4-} Tetraethylbenzenes 50 1,2,4,5-} Tetraethylbenzenes			(70)
Toluene	Propylene	70	*p*-Cymene			(9)
Benzene	Propylene	70	65 *m*-Diisopropylbenzene			(9)
Benzene	Propylene	70	75 1,3,5-Triisopropylbenzene			(9)
Benzene	Ethylene	70 (little $AlCl_3$)	48 1,3,5-Triethylbenzene			(39)
Benzene	Ethylene	70 (much $AlCl_3$)	62–65 1,3,5-Triethylbenzene			(39)
Benzene	Ethylene	55	15 1,3,5-Triethylbenzene			(39)
Benzene	Ethylene	95	62–65 1,3,5-Triethylbenzene			(39)
Toluene	*n*-C_4H_9Cl	0 to 5	75 *m*-, 25 *p*-*sec*-Butyltoluene			(63)
Toluene	Iso-C_4H_9Br	0 to 5	70 *m*-, 30 *p*-*tert*-Butyltoluene			(63)
Toluene	*tert*-C_4H_9Cl	0 to 5	62 *m*-, 38 *p*-*tert*-Butyltoluene			(63)
Toluene	*tert*-C_4H_9Cl (with $C_6H_5NO_2$)	0 to 5	67 *m*-, 33 *p*-*tert*-Butyltoluene			(63)
Toluene	*tert*-C_4H_9Cl		Mostly *m*-*tert*-butyltoluene			(8, 15, 49, 53)

(b) Other catalysts

AROMATIC	ALIPHATIC	CATALYST	PRODUCTS	REFERENCES
Benzene	Propylene	BF_3, H_2SO_4	98 *p*-, 2 *o*-Diisopropylbenzene	(67)
Benzene	Propylene	BF_3, H_2SO_4	1,2,4-Triisopropylbenzene	(67)
Benzene	Propylene	BF_3, H_2SO_4	1,2,4,5-Tetraisopropylbenzene	(67)
Toluene	*tert*-C_4H_9Cl	$FeCl_3$	67 *m*-, 33 *p*-*tert*-Butyltoluene	(63)
Toluene	*tert*-C_4H_9Cl	$FeCl_3$	Mostly *p*-*tert*-butyltoluene	(10, 15, 49, 53)
Benzene	Propylene	H_3PO_4	7 *o*-, 43 *m*-, 50 *p*-Diisopropylbenzene	(41)

* Numbers are percentages adjusted to total 100 per cent for the group of isomers comprising the fraction.

analyses, for illustration. Divergencies from equilibrium composition seem to be on the side of directive influence, and probably indicate incomplete redistribution. Several such differences appear to result from differences in temperature or other factors in vigor of reaction. The very substantial difference between the results using aluminum chloride and ferric chloride in forming *tert*-butyltoluenes is doubtless due to the greater vigor of the former catalyst. It gives largely the meta isomer (8, 15, 49, 53), while ferric chloride gives mostly the para isomer (10, 15, 49, 53), more nearly according to directive influence. On the other hand, Shoesmith and McGechen (63) found little difference between the results with the two catalysts, perhaps because they compensated in some way for the difference in activity of the catalysts.

TABLE 3

Isomerization of alkylbenzenes

ALKYLBENZENE	PRODUCT*	REFERENCES
(a) Catalyst: aluminum chloride		
o-Xylene	18.7 *m*-Xylene	(50)
p-Xylene	64.3 *m*-Xylene	(50)
p-Xylene	Mostly *m*-xylene	(44)
o- and *p*-Xylenes	Mostly *m*-xylene	(29)
Prehnitene	83 Isodurene, 17 durene	(48)
1,2,4-Triethylbenzene 1,3,5-Triethylbenzene	20 1,2,4-Triethylbenzene† 80 1,3,5-Triethylbenzene†	(48)
1,2,3,4-Tetraethylbenzene	50 1,2,3,5-Tetraethylbenzene 50 1,2,4,5-Tetraethylbenzene	(48)
p-Di-*n*-propylbenzene	65 *m*-Di-*n*-propylbenzene	(7)
m-Di-*n*-propylbenzene	Mostly *m*-di-*n*-propylbenzene	(7)
1,2,4-Tri-*n*-propylbenzene	Mostly 1,3,5-tri-*n*-propylbenzene	(7)
1,3-Dimethyl-4-*n*-butylbenzene	1,3-Dimethyl-5-*sec*-butylbenzene	(47)
1,3-Dimethyl-4-*sec*-butylbenzene	1,3-Dimethyl-5-*tert*-butylbenzene	(47)
1,3-Dimethyl-4-*tert*-butylbenzene	1,3-Dimethyl-5-*tert*-butylbenzene	(47)
(b) Catalyst: oleum (Jacobsen reaction)		
Durene Isodurene	Only prehnitene	(43, 69)
1,2,3,5-Tetraethylbenzene 1,2,4,5-Tetraethylbenzene	Only 1,2,3,4-tetraethylbenzene	(71)

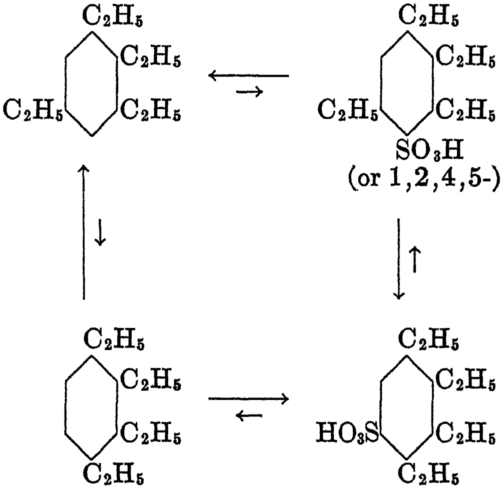
* Numbers are percentages adjusted to total 100 per cent for the group of isomers comprising the fraction.

† Average value.

If the distribution of products under vigorous alkylation is governed largely by equilibria, it is no longer necessary to postulate an arbitrary indirect mechanism. However, some anomalous observations require explanation.

The tetraalkyl isomer to be expected from directive influence is the 1,2,4,5-structure, and this is generally present. It is the only isomer identified from the propylation of benzene (9, 27, 67); but isomerization studies on the tetraethylbenzenes (48) with aluminum chloride catalyst indicate that at equilibrium the 1,2,3,5-isomer is present in equal amount, and for the tetramethylbenzenes it constitutes 83 per cent. The vicinal isomer, 1,2,3,4-, is practically absent in all cases. On the other hand, the Jacobsen rearrangement with oleum catalyst gives almost exclusively the vicinal isomer with both methyl (69) and ethyl groups (71). These observations seem mutually contradictory.

However, it has been shown (43, 69, 71) that it is the sulfonic acid and not the hydrocarbon which isomerized in the Jacobsen reaction. To reconcile the much higher thermodynamic stability of the sulfonic acid of the vicinal derivative than those of its isomers with the much lower stability of the free hydrocarbon (or of its aluminum chloride complex), it is necessary to postulate a much higher equilibrium in sulfonating the vicinal, as indicated by the length of arrows in the following scheme:



Another example of the effect of strong sulfuric acid in modifying the reaction is the production of 2,6-diisopropyltoluene (17), an isomer which could hardly be expected from aluminum chloride catalysis. The latter rarely gives vicinal isomers if it is possible for the alkyl groups to be further apart. Presumably a sulfonic acid had blocked off the para position and augmented directive influence to the 2- and 6-positions.

Closely related to orientation is the effect of substituents on the absolute rate of further substitution. It is well known that toluene and other alkylbenzenes are more readily nitrated or halogenated than benzene. Aniline, phenol, and their derivatives are still more reactive. On the other hand, a nitro or carboxyl group greatly retards substitution. This effect is not quite parallel with directive influence, since halogen substituents make a benzene ring less reactive although they are ortho–para directing. Moreover, in a mixture of toluene and chlorobenzene the former is much more reactive to nitration (79), although in *o*-chlorotoluene the directive power of chlorine predominates over that of methyl. The distinction has been discussed previously (19, pages 277–80).

Similar effects have been noted in alkylation, to such an extent that it has not been found possible to alkylate nitrobenzene or benzoic acid (16). *p*-Dichlorobenzene was found sufficiently inert (50) to aluminum bromide for molecular weight determinations of toluene complexes with the catalyst, although it has been ethylated (21). Ethylation of 1,2,4-trichlorobenzene was effected to only a slight extent under conditions giving high-speed ethylation of benzene (21). The effect of ethyl groups upon the rate of further ethylation has been shown in this paper and previously (22) to be almost negligible. However, propylation was found to be slightly accelerated by alkyl groups in the molecule (16a).

REFERENCES

(1) Ador, E., and Rilliet, A. A.: Ber. **11**, 1627 (1878).
(2) American Petroleum Institute Research Project 44 at the National Bureau of Standards. Selected Values of Properties of Hydrocarbons. Tables 5y, 24y. November 30, 1945.
(3) Amos, J. L.: U. S. patent 2,225,543 (1940).
(4) Anschütz, R.: Ann. **235**, 189 (1886).
(5) Anschütz, R., and Immendorff, H.: Ber. **18**, 657 (1885).
(6) Aston, J. G.: Ind. Eng. Chem. **34**, 520 (1942).
(7) Baddeley, G., and Kenner, J.: J. Chem. Soc. **1935**, 303.
(8) Baur, A.: Ber. **24**, 2832 (1891).
(9) Berry, T. M., and Reid, E. E.: J. Am. Chem. Soc. **49**, 3142 (1927).
(10) Bialobrzeski, M.: Ber. **30**, 1773 (1897).
(11) Boedtker, E.: Bull. soc. chim. [3] **35**, 835 (1906).
(12) Boedtker, E., and Halse, O. M.: Bull. soc. chim. [4] **19**, 444 (1916).
(13) Bowden, E.: J. Am. Chem. Soc. **60**, 645 (1938).
(14) Burwell, R. L., Jr., and Archer, S.: J. Am. Chem. Soc. **64**, 1032 (1942).
(15) Buu-Hoï, N. G., and Cagnaint, P.: Bull. soc. chim. [5] **9**, 887, 889 (1942); Chem. Abstracts **38**, 2937 (1944).
(16) Calloway, N. O.: Chem. Revs. **17**, 327 (1935).
(16a) Condon, F. E.: J. Am. Chem. Soc. **70**, 2265 (1948).
(17) Desseigne, G.: Compt. rend. **200**, 466 (1935).
(18) Eyring, H., Hulburt, H. M., and Harman, R. A.: Ind. Eng. Chem. **35**, 516 (1943).
(19) Francis, A. W.: Chem. Revs. **3**, 257 (1926).
(20) Francis, A. W.: Chem. Revs. **42**, 107 (1948).
(21) Francis, A. W.: Unpublished work in this laboratory.
(22) Francis, A. W., and Reid, E. E.: Ind. Eng. Chem. **38**, 1194 (1946).
(23) Friedel, C., and Crafts, J. M.: Compt. rend. **84**, 1392 (1877); Brit. Chem. Abstracts **32**, 725.
(24) Gilman, H., and Meals, R. N.: J. Org. Chem. **8**, 126 (1943).
(25) Gilman, H., and Turck, J. A. V., Jr.: J. Am. Chem. Soc. **61**, 478 (1939).
(26) Given, P. H., and Hammick, D. L.: J. Chem. Soc. **1947**, 928.
(27) Grosse, A. V., and Ipatieff, V. N.: J. Org. Chem. **2**, 447 (1937).
(28) Hansford, R. C., Myers, C. G., and Sachanen, A. N.: Ind. Eng. Chem. **37**, 671 (1945).
(29) Heise, R., and Töhl, A.: Ann. **270**, 155 (1892).
(30) Holleman, A. F.: Rec. trav. chim. **37**, 195 (1918); Chem. Abstracts **13**, 569 (1919).
(31) Huston, R. C., and Kaye, I. A.: J. Am. Chem. Soc. **64**, 1576 (1942).
(32) Ipatieff, V. N., and Pines, H.: J. Am. Chem. Soc. **59**, 56 (1937).
(33) Ipatieff, V. N., Pines, H., and Schmerling, L.: J. Am. Chem. Soc. **60**, 353 (1938).
(34) Ipatieff, V. N., Pines, H., and Schmerling, L.: J. Org. Chem. **5**, 253 (1940).

(35) Jacobsen, O. G.: Ber. **14,** 2624 (1881).
(36) Jacobsen, O. G.: Ber. **18,** 338 (1885).
(37) Legge, D. I.: J. Am. Chem. Soc. **69,** 2079 (1947).
(38) Linstead, R. P.: Ann. Repts. Progress Chem. (Chem. Soc. London) **34,** 259 (1937).
(39) Marks, E. M., Almand, J. M., and Reid, E. E.: J. Org. Chem. **9,** 13 (1944).
(40) Mattox, W. J.: U. S. patent 2,360,814 (1944).
(41) Melpolder, F. W., Woodbridge, J. E., and Headington, C. E.: J. Am. Chem. Soc. **70,** 935 (1948).
(42) Milligan, C. H., and Reid, E. E.: J. Am. Chem. Soc. **44,** 206 (1922); Ind. Eng. Chem. **15,** 1048 (1923).
(43) Moyle, C. L., and Smith, L. I.: J. Org. Chem. **2,** 112 (1937).
(44) Mundici, C. M.: Gazz. chim. ital. **34,** ii, 114 (1904); Brit. Chem. Abstracts **86,** i, 897.
(45) Natelson, S.: Ind. Eng. Chem. **25,** 1391 (1933).
(46) Nightingale, D. V.: Chem. Revs. **25,** 329 (1939).
(47) Nightingale, D. V., and Smith, L. I.: J. Am. Chem. Soc. **61,** 101 (1939).
(48) Nightingale, D. V., and Wadsworth, F.: J. Am. Chem. Soc. **63,** 3514 (1941).
(49) Noelting, E.: Chimie & industrie **6,** 722 (1921).
(50) Norris, J. F., and Rubinstein, D.: J. Am. Chem. Soc. **61,** 1163 (1939).
(51) Norris, J. F., and Vaala, G. T.: J. Am. Chem. Soc. **61,** 2131 (1939).
(52) O'Kelly, A. A., Kellett, J., and Plucker, J.: Ind. Eng. Chem. **39,** 154 (1947).
(53) Pajeau, R.: Bull. soc. chim. [5] **12,** 637 (1945).
(54) Pines, H., Schmerling, L., and Ipatieff, V. N.: J. Am. Chem. Soc. **62,** 2901 (1940).
(55) Pitzer, K. S., and Scott, D. W.: J. Am. Chem. Soc. **65,** 813 (1943).
(56) Price, C. C.: Chem. Revs. **29,** 44, 64 (1941).
(57) Price, C. C.: *Organic Reactions*, Vol. III, Chap. I. John Wiley and Sons, Inc., New York (1946).
(58) Price, C. C., and Ciskowski, J. M.: J. Am. Chem. Soc. **60,** 2501 (1938).
(59) Price, C. C., and Lund, M.: J. Am. Chem. Soc. **62,** 3105 (1940).
(60) Rudkovskiĭ, D. M., Trifel, A. G., and Frost, A. W.: Ukrain. Khem. Zhur. **10,** Wiss. Teil 277 (1935); Chem. Zentr. **1936, I,** 3667.
(61) Schorger, A. W.: J. Am. Chem. Soc. **39,** 2671 (1917).
(62) Schultze, W. A.: U. S. patents 2,382,505 and 2,382,506 (1945).
(63) Shoesmith, J. B., and McGechen, J. F.: J. Chem. Soc. **1930,** 2231.
(64) Simons, J. H., Archer, S., and Adams, E.: J. Am. Chem. Soc. **60,** 2955 (1938).
(65) Simons, J. H., and Hart, H.: J. Am. Chem. Soc. **66,** 1309 (1944).
(66) Simons, J. H., and Hart, H.: J. Am. Chem. Soc. **69,** 979 (1947).
(67) Slanina, S. J., Sowa, F. J., and Nieuwland, J. A.: J. Am. Chem. Soc. **57,** 1547 (1935).
(68) Smith, L. I., and Cass, O. W.: J. Am. Chem. Soc. **54,** 1609 (1932).
(69) Smith, L. I., and Cass, O. W.: J. Am. Chem. Soc. **54,** 1614 (1932).
(70) Smith, L. I., and Guss, C. O.: J. Am. Chem. Soc. **62,** 2625 (1940).
(71) Smith, L. I., and Guss, C. O.: J. Am. Chem. Soc. **62,** 2631 (1940).
(72) Smith, L. I., and Perry, H. O.: J. Am. Chem. Soc. **61,** 1411 (1939).
(73) Thomas, C. A.: *Anhydrous Aluminum Chloride in Organic Chemistry*, pp. 77–104, 459–63. Reinhold Publishing Corporation, New York (1941).
(74) Tilicheev, M. D., and Kuruindin, K. S.: Neftyanoe Khoz. **19,** 586 (1930); Chem. Zentr. **1931, I,** 2560.
(75) Tilman, G.: Thesis, Amsterdam, 1928; through Rec. trav. chim. **53,** 544 (1934).
(76) Tsukervanik, I. P.: J. Gen. Chem. (U.S.S.R.) **15,** 699 (1945); U.O.P. Survey Foreign Petroleum Literature, Translation 612, July 26, 1946; Chem. Abstracts **40,** 5707 (1946).
(77) Verley A.: Bull. soc. chim. [3] **19,** 67 (1898).
(78) Welch, C. E., and Hennion, G. F.: J. Am. Chem. Soc. **63,** 2603 (1941).
(79) Wibaut, J. P.: Rec. trav. chim. **32,** 244 (1913); **34,** 241 (1915); Chem. Abstracts **8,** 1268 (1914); **10,** 184 (1916).

BROMINATIONS WITH N-BROMOSUCCINIMIDE AND RELATED COMPOUNDS

THE WOHL-ZIEGLER REACTION

CARL DJERASSI

Research Department, Division of Chemistry, Ciba Pharmaceutical Products, Inc., Summit, New Jersey

Received January 16, 1948

CONTENTS

I. Historical 271
II. The scope and present limitations of the Wohl-Ziegler reaction 272
  A. Introduction 272
  B. Monoölefins 273
    1. Aliphatic and alicyclic olefins 273
    2. Isoprenoids 275
    3. Steroids 275
  C. Polyolefins 278
    1. Non-conjugated 278
    2. Conjugated 280
  D. Carbonyl compounds 282
  E. Compounds with functional groups (other than carbonyl) alpha or beta to a double bond 285
  F. Aromatic hydrocarbons 287
    1. Nuclear bromination 287
    2. "Side chain" bromination 288
  G. Heterocyclic compounds 289
III. The mechanism of the reaction 291
IV. Experimental conditions 293
  A. *N*-Bromoimides 293
  B. Solvents 293
  C. Molar proportions 294
  D. Temperature 294
  E. Catalysts 294
  F. General procedure for Wohl-Ziegler reaction 295
V. Conclusion 295
VI. Tables 296
VII. References 296
VIII. Appendix 314

I. HISTORICAL

In contrast to the well-known addition of halogen to the double bond, it was only in 1919 that the first report by Wohl (99) appeared on an apparently general method for the direct introduction of a halogen atom (bromine) in the "allyl position" of an olefin.

$$—CH{=}CH—CH_2— \rightarrow —CH{=}CH—CHX—$$

rather than

$$—CHX—CHX—CH_2—$$

Wohl's papers (99, 100), although unusual, did not attract much attention, partly because the reagent used, *N*-bromoacetamide, was not too readily available, but chiefly because in his work the theoretical rather than practical aspects of this reaction were emphasized. The same result, i.e., substitution of the methylene group rather than addition of halogen to the double bond, has been accomplished by direct halogenation of simple low-molecular-weight olefins (31), particularly at high temperatures, but this method is only of very limited general applicability and will not be discussed in this review. In 1942, Ziegler and his collaborators (103) published their extensive research on the allylic bromination of olefins, in which they introduced the unique brominating agent *N*-bromosuccinimide. Their findings, which emphasized the preparative nature of this reaction, were employed almost immediately by organic chemists, as demonstrated by the relatively large literature which has already accumulated on the subject during the past five years.

In the meantime, a number of workers have introduced the use of catalysts in conjunction with *N*-bromoimides and have applied these reagents to brominations of aromatic and ketonic substances, thus extending appreciably the scope of the reaction as envisaged originally by Wohl and Ziegler. This review of the Wohl–Ziegler reaction, as the bromination with *N*-bromoimides will be referred to, has been written primarily with its synthetic applications in mind and to direct attention to those aspects of the reaction which still have to be investigated.

II. THE SCOPE AND PRESENT LIMITATIONS OF THE WOHL–ZIEGLER REACTION

A. INTRODUCTION

Wohl (99, 100) showed that *N*-bromoacetamide[1] reacted in the cold in ether or acetone solution over a period of several hours or days with olefins (such as with 2,3-dimethyl-2-butene to give about 16 per cent of 1-bromo-2,3-dimethyl-2-butene), with anisole to yield 75 per cent of *p*-bromoanisole, and with ethyl acetoacetate to give a 45 per cent yield of the corresponding α-bromo derivative. In the latter case, *N*-bromophthalimide could be substituted for *N*-bromoacetamide. During the next twenty-three years only isolated examples (89, 95, 101) of the use of *N*-bromoacetamide in anhydrous media[1] were reported.

Ziegler and coworkers (103), in connection with their work on cantharidin (102), carried out an extensive search for a halogenating agent for olefins which would not attack the double bond but would substitute in the α-methylenic or "allyl position." The feasibility of such a reaction had already been demonstrated by Wohl's earlier work, as well as by other examples in which attack in the allyl position had been observed, as in the case of various oxidizing agents, dienophiles, etc. (summarized in references 1, 25, 103). However, it was necessary to find a reagent which would fulfill all or most of the following requirements: (*a*) it should be stable and readily available; (*b*) it should effect "allylic halogenation" with a minimum of side reactions; (*c*) the halogen carrier should be of relatively low molecular weight and recoverable (it was obvious that with few exceptions (31) free halogens could not be employed); (*d*) preferably, it should react in an inert solvent.

---

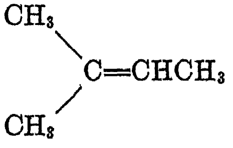
[1] Reactions of *N*-bromoacetamide in aqueous solution usually involve the formation of hypobromous acid and do not fall within the scope of this review (for leading references see 85 and 103).

In 1942, in a detailed empirical study, Ziegler *et al.* (103) reported that *N*-bromosuccinimide met practically all the requirements enumerated above. *N*-Bromophthalimide, already employed by Wohl (100), was fairly satisfactory, while *N*-chlorosuccinimide, *N*-bromoglutarimide, and *N*-bromohexahydrophthalimide could not be used in this type of reaction. Certain *N*-chloroacylanilides and *N*-chloroamides (but not sulfonamides or imides) showed some promise as chlorinating agents, but were not studied in detail and have not found any general applicability, since they were inferior to *N*-bromosuccinimide as halogenating agents. The experimental conditions are considered in detail in Section IV, but in general with *N*-bromosuccinimide, the reagent is refluxed in carbon tetrachloride with the substance to be brominated until all the reagent has been consumed.

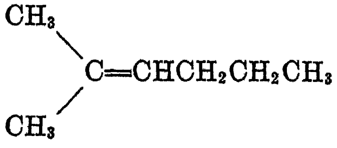
B. MONOÖLEFINS

1. *Aliphatic and alicyclic olefins*

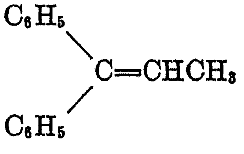
As mentioned above, Wohl (99) studied the bromination with *N*-bromoacetamide of a few simple olefins, such as 2,3-dimethyl-2-butene. Ziegler (103), in a more extensive study, found that with few exceptions *N*-bromosuccinimide reacted much more readily with a methylene than a methyl group and that tertiary hydrogen atoms in general were not attacked. Thus, 2-methyl-2-butene (I) required 16 hr. for completion of the reaction, while with 2-methyl-2-hexene (II) the reaction was finished after 10 min. A similar relationship was observed with the diphenylolefins III and IV.



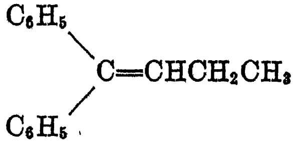
I



II

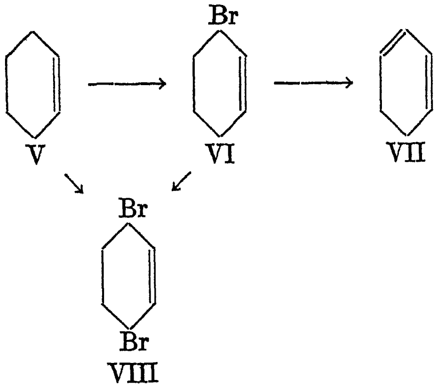


III



IV

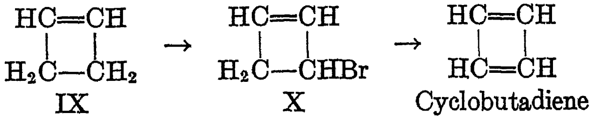
With cyclohexene (V), the 3-bromo derivative (VI) was obtained in high yield in about 20 min. and on dehydrobromination with quinoline it afforded 80–90 per cent of 1,3-cyclohexadiene (VII), undoubtedly the simplest method for preparing this compound.



With *N*-bromophthalimide instead of *N*-bromosuccinimide, the yield of VI was lowered to about 50 per cent and appreciable amounts of the adduct of cyclohexene and *N*-bromophthalimide were isolated. The dibromination of cyclohexene to VIII proceeded very unsatisfactorily when an excess of *N*-bromosuccinimide was treated with cyclohexene, but much more readily when 1 mole of *N*-bromosuccinimide was allowed to act upon the monobromo compound (VI). Ziegler's explanation for this difference is given below in Section III. More recently, Howton (36) made a detailed study of this reaction in the presence of peroxide and has isolated, in addition to VI, small amounts of VIII and of 1,2-dibromocyclohexane. The latter possibly arose from the reaction of free bromine, formed from *N*-bromosuccinimide and hydrogen bromide (probably liberated by spontaneous dehydrobromination of VI). With an excess of *N*-bromosuccinimide, V yields brominated benzene derivatives (5).

While only one monosubstitution product is possible in the case of cyclohexene, several products could be formed with substituted cyclohexenes. Mousseron *et al.* (61) examined the action of *N*-bromosuccinimide on several substituted cyclohexenes and cyclopentenes. Whereas 1-alkyl-1-cyclohexenes yielded predominantly the 6-bromo derivative, the corresponding 1-chloro derivative gave the 3-isomer. All the possible methylcyclohexenes as well as a few other compounds were studied, and the results are given in table 1. Cyclopentenes seem to react similarly.

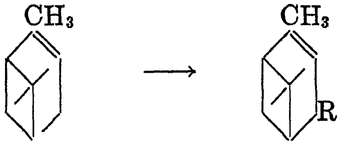
Baker (3) in his Tilden lecture suggested that a promising approach to the solution of the cyclobutadiene problem would be the application of the Wohl-Ziegler reaction to cyclobutene (IX) affording the 3-bromo derivative (X), which on removal of hydrogen bromide, either directly or by treating X with dimethylamine and applying the exhaustive methylation procedure, should lead to cyclobutadiene. This suggestion has been tested experimentally by Howton and Buchman (37), who obtained traces of the desired 3-bromocyclobutene (X), the major product being 1,2-dibromocyclobutane. Results with methylenecyclobutane are shown in table 1.



$$\begin{array}{ccccc} \mathrm{HC{=}CH} & & \mathrm{HC{=}CH} & & \mathrm{HC{=}CH} \\ |\quad\;\; | & \rightarrow & |\quad\;\; | & \rightarrow & |\quad\;\; | \\ \mathrm{H_2C{-}CH_2} & & \mathrm{H_2C{-}CHBr} & & \mathrm{HC{=}CH} \\ \mathrm{IX} & & \mathrm{X} & & \text{Cyclobutadiene} \end{array}$$

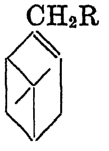
2. *Isoprenoids*

Ziegler (103) reported the successful bromination of α-pinene (XI) with *N*-bromosuccinimide to give an unknown monobromopinene. The reaction has recently been reinvestigated by Buu-Hoï and coworkers (14), who assigned to the product the structure XIIa rather than the alternate XIIIa, since it was not identical with the product formed in the reaction of *l*-myrtenol (XIIIb) with phosphorus tribromide. It should be pointed out that an authentic sample of bromopinene from *l*-verbenol (XIIb) was not prepared.



XI

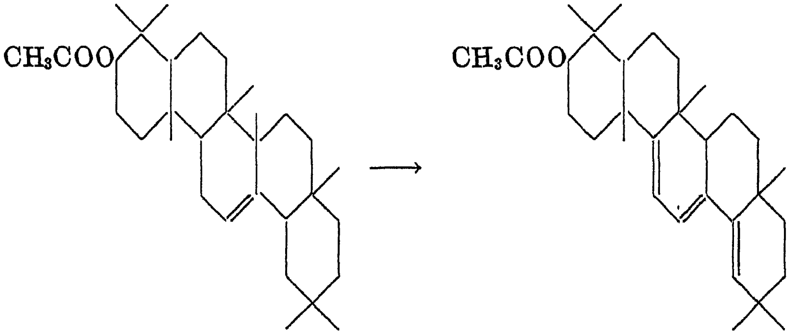
XIIa (R = Br)
XIIb (R = OH)



XIIIa (R = Br)
XIIIb (R = OH)

Apparently, this reaction follows Ziegler's rule in that a methylene group is attacked in preference to a methyl group.

Ruzicka and Plattner (63, 79, 80) have employed the Wohl–Ziegler reaction extensively in their work on steroids and terpenes. Among the reactions studied, this has led to an improved procedure for norcedrenedicarboxylic acid (63), as well as to the introduction of double bonds into the amyrin molecule (79). Thus when β-amyrin acetate (XIV) was refluxed in carbon tetrachloride solution with an excess of *N*-bromosuccinimide for 2 hr., dibromination occurred followed by loss of hydrogen bromide, resulting in an excellent yield of β-amyratrienol acetate (XV). The corresponding reaction with the benzoate gave poorer results (62). Other examples of mono-unsaturated isoprenoids are considered in table 1.



XIV
β-Amyrin acetate

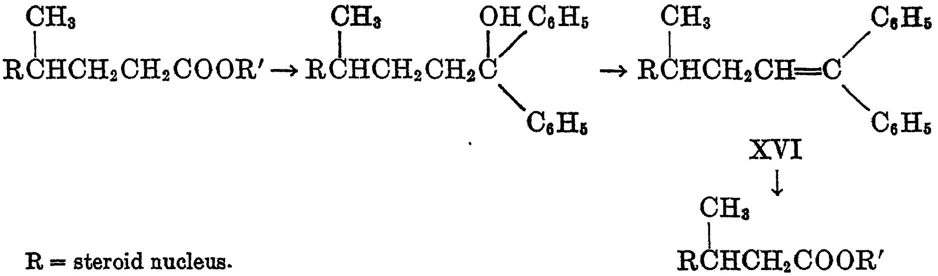
XV
β-Amyratrienol acetate

Roberts and Trumbull (124) studied the reaction of camphene and norbornylene, where allylic bromination is possible only at the bridge-head positions. Camphene gave predominantly the vinyl bromide (ω-bromocamphene), while norbornylene yielded the 7-bromo derivative (*cf.* table 1).

3. *Steroids*

The application of the Wohl–Ziegler reaction to steroid chemistry has been one of the most striking examples of its usefulness and is mainly due to Meystre, Miescher, Wettstein, and their coworkers (49–58, 96, 97).

An important problem in steroid chemistry has been the degradation of the bile acid side chain to the "methyl ketone," "etio acid," and "17-ketone" stages, which in turn represent intermediates for the synthesis of the progestational, cortical, and androgenic hormones. The conventional and very tedious method has been the classical Barbier–Wieland degradation, which removed one carbon atom at a time by formation of the diphenylcarbinol, followed by dehydration and oxidation.

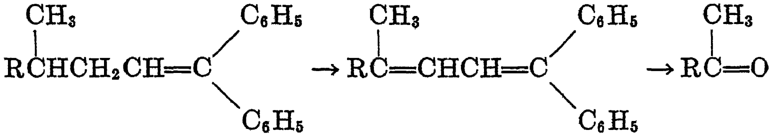


$$R\overset{CH_3}{\overset{|}{C}}HCH_2CH_2COOR' \rightarrow R\overset{CH_3}{\overset{|}{C}}HCH_2CH_2\overset{OH}{\overset{|}{C}}(C_6H_5)_2 \rightarrow R\overset{CH_3}{\overset{|}{C}}HCH_2CH{=}C(C_6H_5)_2 \;(\text{XVI}) \rightarrow R\overset{CH_3}{\overset{|}{C}}HCH_2COOR'$$

XVI

R = steroid nucleus.

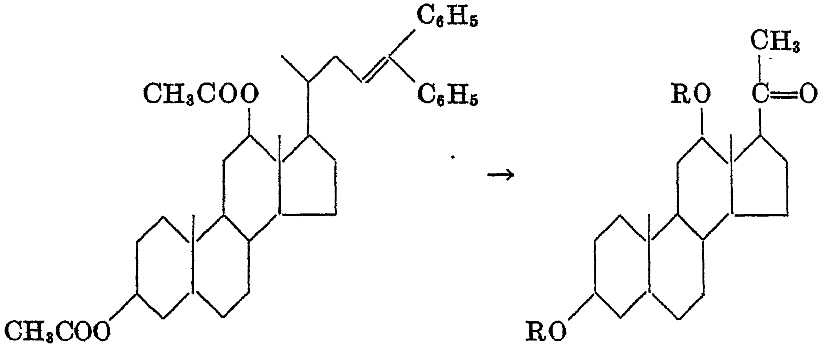
Meystre and coworkers (49), and independently Ettlinger and Fieser (24), found that the diphenylethylene derivative (XVI) could be brominated with *N*-bromosuccinimide, the elements of hydrogen bromide eliminated, and the resulting crude diene (XVII) oxidized to remove three carbon atoms in essentially one step, leading directly to the "methyl ketone" stage (XVIII).



$$\underset{\text{XVI}}{R\overset{CH_3}{\overset{|}{C}}HCH_2CH{=}C(C_6H_5)_2} \rightarrow \underset{\text{XVII}}{R\overset{CH_3}{\overset{|}{C}}{=}CHCH{=}C(C_6H_5)_2} \rightarrow \underset{\text{XVIII}}{R\overset{CH_3}{\overset{|}{C}}{=}O}$$

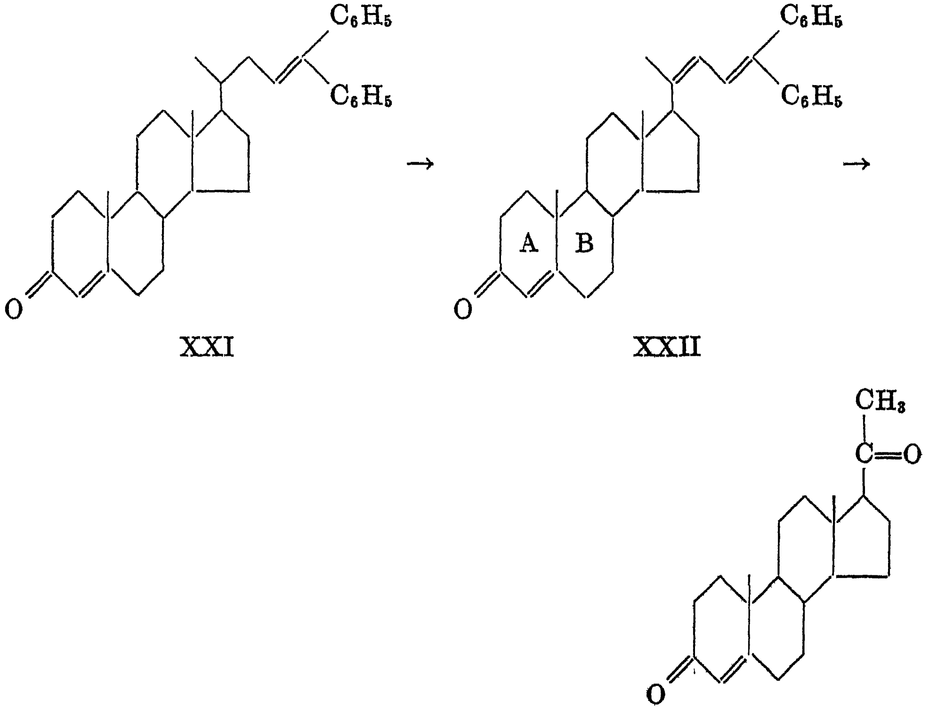
XVI XVII XVIII

The initial attempts were carried out in the usual manner with Δ^{23}-3(α),12(α)-diacetoxy-24,24-diphenylcholene (XIX) and gave about 25 per cent of the methyl ketone XX without isolation of intermediates. This represented already a major advance over the corresponding Barbier–Wieland degradation, which required seventeen steps and afforded the methyl ketone in 7 per cent overall yield.



XIX XX

The Swiss workers soon discovered (50) that exposure to strong light had a powerful catalytic effect and that yields of 82 per cent of pure diene could be realized with either *N*-bromosuccinimide or *N*-bromophthalimide. The bromination was complete after about 15 min., but refluxing was continued for 4 hr., hydrogen bromide being eliminated during that period. The recognition of photocatalysis in the Wohl–Ziegler reaction extended appreciably the scope of the reaction, as will become apparent from the succeeding sections. The same investigators in a series of papers (51, 52, 53, 56) applied their photocatalytic method to a number of bile acids with various substituents in the steroid nucleus. Starting from 3(β)-hydroxycholenic acid, they developed six synthetic routes, all involving the Wohl–Ziegler reaction, which led to the important hormone progesterone (XXIII). Perhaps the most interesting method from the standpoint of the selectivity of the Wohl–Ziegler reaction involves as the starting material the unsaturated ketone XXI (56). In the presence of light, XXI reacted with *N*-bromosuccinimide almost exclusively in the side chain to give the intermediate XXII (after dehydrobromination with dimethylaniline) without attack in ring A or B (see Section D below; also 19, 54). After oxidative removal of the side chain, progesterone (XXIII) was obtained in 32 per cent over-all yield based on XXI without isolation of intermediates.



XXI

XXII

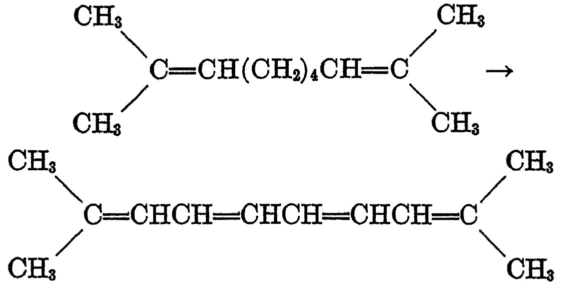
XXIII

Moffett and coworkers (59) employed this method for the degradation of hyodesoxycholic acid.

C. POLYOLEFINS (SEE TABLE 2)

1. Non-conjugated

In the single case studied by Ziegler (103), 2,9-dimethyl-2,8-decadiene reacted nearly quantitatively with 2 moles of *N*-bromosuccinimide, but the dehydrobromination product, the tetraene, was obtained only in an impure state.



$$(CH_3)_2C{=}CH(CH_2)_4CH{=}C(CH_3)_2 \rightarrow$$

$$(CH_3)_2C{=}CHCH{=}CHCH{=}CHCH{=}C(CH_3)_2$$

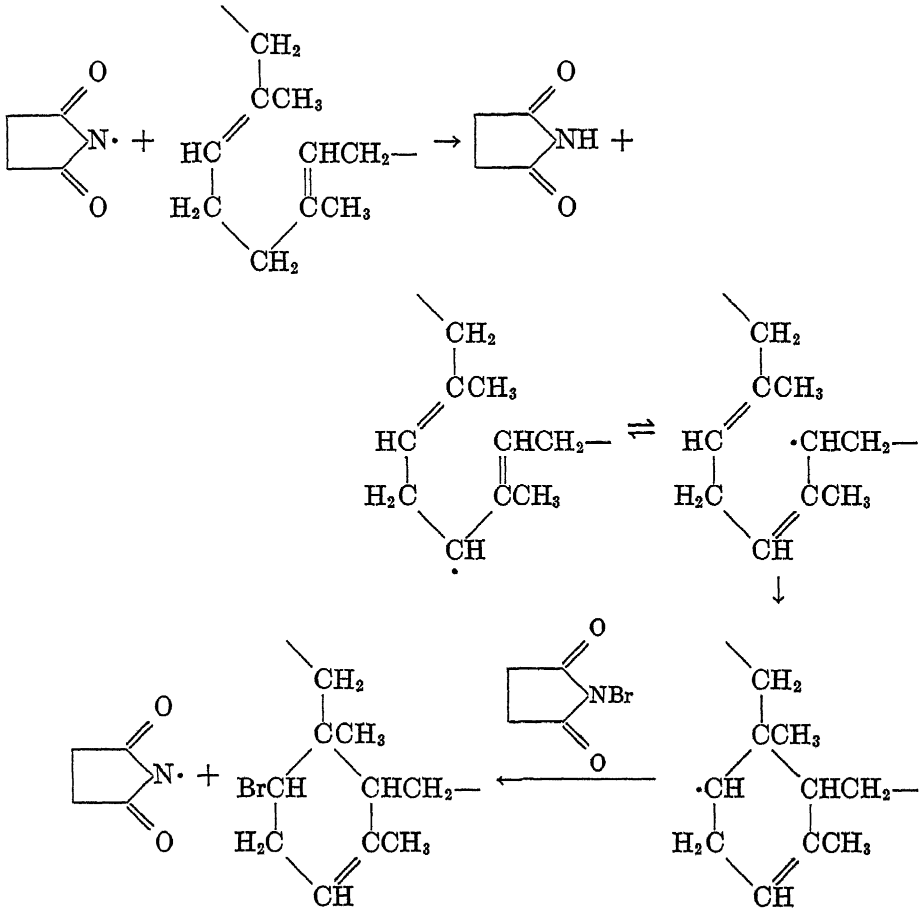
Recent work by Schmid and Karrer (86), who have introduced the use of dibenzoyl peroxide as catalyst in the Wohl–Ziegler reaction, still further extended the scope of the method which Ziegler thought to have reached in the case of the decadiene. These workers have shown that a number of brominations, previously unsuccessful with *N*-bromosuccinimide (such as the bromination of tertiary hydrogen atoms, the side chain of toluene, conjugated dienes), could be accomplished readily when a small amount of peroxide was added to the reaction mixture, often in conjunction with strong light.

Using this new extension, Karrer and Ringli (43) have studied the bromination of diallyl (XXIV) with *N*-bromosuccinimide. In the presence of peroxide and light, after refluxing for about 8 hr., diallyl (1,5-hexadiene) gave a monobromo compound to which was assigned the structure XXV and which readily reacted with silver acetate or alcoholic alkali. Further bromination of the monobromo compound with *N*-bromosuccinimide led to a dibromo compound, considered to be 3,4-dibromo-1,5-hexadiene, which was convertible to a diacetate and similar derivatives. More recent work (44) has shown, however, that the dibromo compound possessed the isomeric structure XXVI resulting from two allylic rearrangements, and that the monobromo compound (117) should be represented by XXV as believed originally, rather than by one of the other two possible allylic structures. Reaction of XXV with silver acetate was shown to be accompanied by rearrangement.

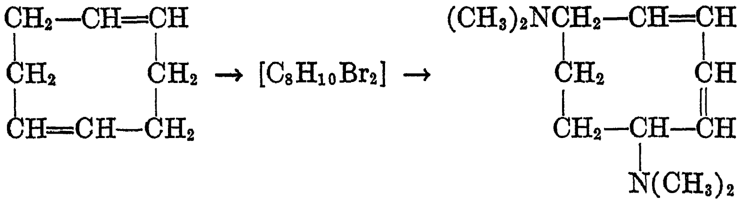
$$\begin{array}{ccc} CH_2{=}CHCH_2CH_2CH{=}CH_2 & \rightarrow & CH_2{=}CHCHBrCH_2CH{=}CH_2 \\ \text{XXIV} & & \text{XXV} \\ & & \downarrow \\ & & BrCH_2CH{=}CHCH{=}CHCH_2Br \\ & & \text{XXVI} \end{array}$$

The possibility of allylic rearrangements in the Wohl–Ziegler reaction should never be overlooked. This has been noted by Ziegler in the dibromination of dodecylene (103) and by others (17, 37, 97).

Bloomfield (7), who observed that dihydromyrcene (2,6-dimethyl-2,6-octadiene) easily gave a monobromo compound with *N*-bromosuccinimide, applied the Wohl-Ziegler reaction to acetone-extracted crepe rubber and obtained bromo-rubber of the empirical formula $(C_{10}H_{15}Br)_x$. Since the iodine number of this bromo-rubber was far below the calculated amount and on the assumption that bromination occurred only in the allyl position, Bloomfield postulated that cyclization occurred during the reaction as depicted below, employing a free-radical mechanism (see also Section III on mechanism).



Another interesting example has been reported by Cope (17), who studied the action of *N*-bromosuccinimide in the presence of peroxide (light had no effect) on 1,5-cyclooctadiene (XXVII), which was obtained from chloroprene dimer. Depending on the molar ratio, a mono or dibromo compound or both were formed. In view of the ample opportunity for allylic rearrangements, definite structures have not yet been assigned to these compounds, but on treatment with dimethylamine the dibromo derivative gave 5,8-bis(dimethylamino)-1,3-cyclooctadiene (XXVIII), an intermediate in the Willstätter synthesis of cyclooctatetraene.

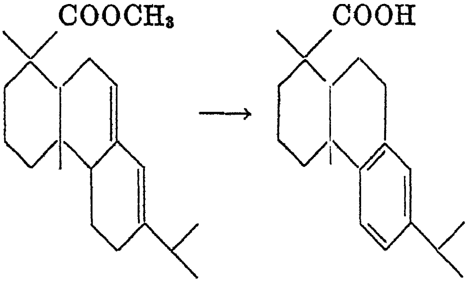


XXVII XXVIII

In the field of carotenoids, Karrer and Rutschmann (39) prepared dehydrolycopene, which possesses fifteen conjugated double bonds, by treating lycopene with 2 moles of *N*-bromosuccinimide, the intermediate dibromo compound losing hydrogen bromide spontaneously. The bromination is formulated as occurring on the methylene groups adjacent to the isolated double bonds rather than to the conjugated system.

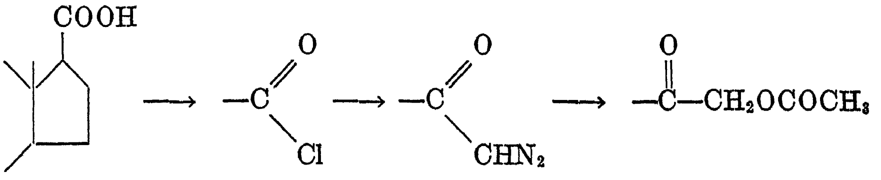
2. Conjugated

Ziegler (103) was unable to isolate any definite product on treating 1,3-cyclohexadiene with *N*-bromosuccinimide and believed that substitution of a methylene group adjacent to a conjugated system of double bonds was beyond the scope of his reaction. This has since been shown to be incorrect (see also Section II,E). For instance, using *N*-bromosuccinimide without catalysts, a new and simplified method for the preparation of dehydroabietic acid (XXX) from methyl abietate (XXIX) in one operation has been reported by Jeger *et al.* (38). The previous synthesis (26) of this interesting compound involved catalytic dehydrogenation and purification through the sulfonic acid.



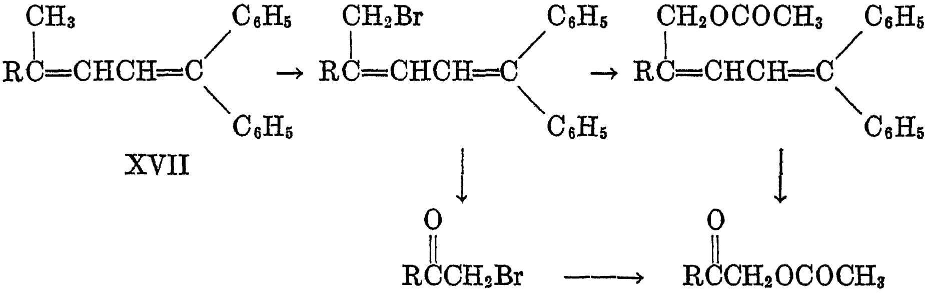
XXIX XXX
Methyl abietate Dehydroabietic acid

An important application of the Wohl-Ziegler reaction has been reported by Meystre and Wettstein (55, 57, 58, 96), who succeeded in adapting their bile acid degradation method to the introduction of the ketol side chain characteristic of the cortical hormones. Prior to their work, the method employed most commonly involved degradation of the sterol side chain to the "etio acid" (XXXI), conversion to the diazo ketone, and reaction with acetic acid. The pertinent literature on this and related methods has been reviewed elsewhere (55).



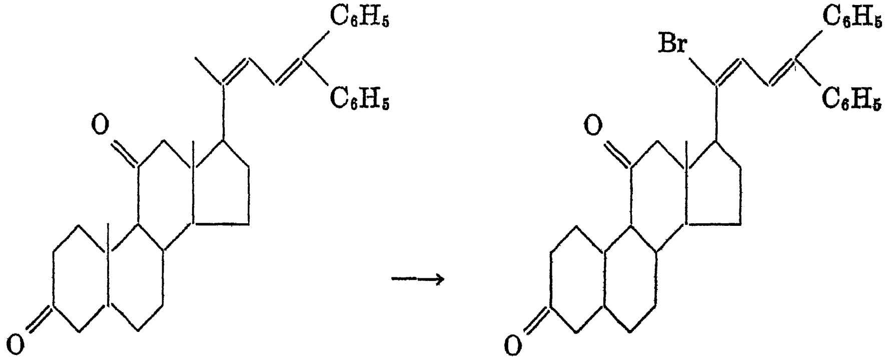
XXXI

These investigators found that preferably, but not necessarily, in the presence of strong light the steroid dienes (XVII) which they had prepared in connection with their work on bile acid degradation, using the Wohl-Ziegler reaction, could be brominated with an additional mole of *N*-bromosuccinimide, the bromine entering in position 21. The bromo compound could then be oxidized, followed by treatment with potassium acetate, or the process could be reversed. It was thus possible to introduce the cortical hormone side chain directly and to eliminate the complete degradation of the sterol or bile acid side chain to the etio acid stage (XXXI).



XVII

The yields of bromo compound were in the neighborhood of 70 per cent in several instances and furthermore, as in the bromination of the steroid ethylenes (Section II,B), the presence of certain reactive groups in the steroid nucleus did not interfere. This led to a new synthesis for 11-desoxycorticosterone (58). An unusual example was $\Delta^{20;23}$-3,11-diketo-24,24-diphenylcholadiene (XXXII), where bromination to XXXIII was accomplished in 62 per cent yield (96). The latter was then converted to the valuable 11-dehydrocorticosterone acetate.

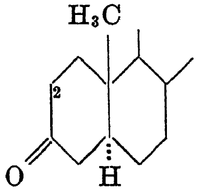


XXXII XXXIII

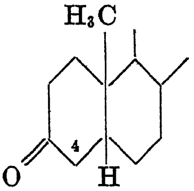
D. CARBONYL COMPOUNDS

Except for the early work of Wohl[2] on the bromination of ethyl acetoacetate with *N*-bromoacetamide (99) and *N*-bromophthalimide (100), it was not until 1946 that publications appeared in which *N*-bromoimides had been employed for the bromination of ketones. The special application of the Wohl–Ziegler reaction to carbonyl compounds will be illustrated below with several examples.

Schmid and Karrer (86) showed that cyclohexanone and certain ketopelargonic acid derivatives readily afforded the corresponding α-bromoketones. Employing strong light and either *N*-bromosuccinimide or *N*-bromophthalimide, it was found recently (19) that saturated 3-ketosteroids of the allo (XXXIV) and normal (XXXV) series reacted in a few minutes to form the 2-bromo and 4-bromo compounds, respectively.

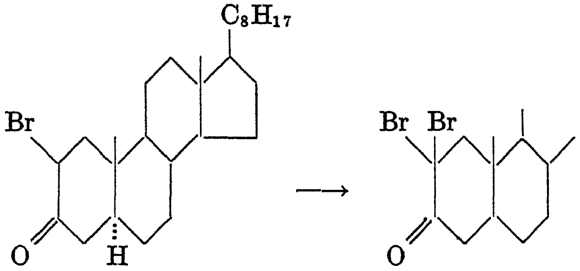


XXXIV



XXXV

Free hydroxyl and carbomethoxyl groups did not seem to interfere. It is apparent, therefore, that the same stereochemical factors are involved with *N*-bromosuccinimide as with bromine in acetic acid. This method may have special application in cases where groups sensitive to bromine or hydrogen bromide are present. For instance, the further bromination of 2-bromocholestanone (XXXVI) with *N*-bromosuccinimide was shown to result in the formation of the 2,2-dibromo compound XXXVII, while with bromine in acetic acid, hydrogen bromide had to be removed to obtain the same results (20).



XXXVI XXXVII

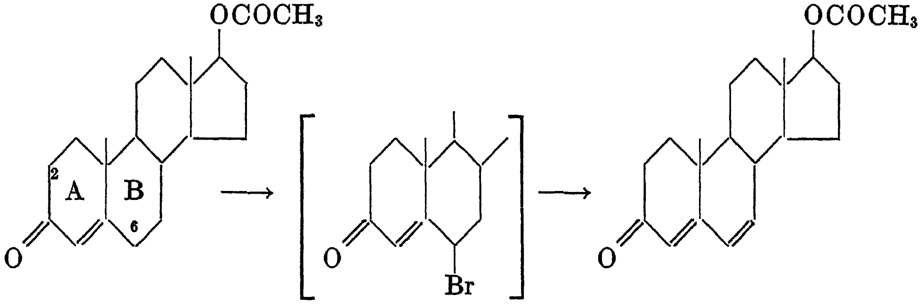
Preliminary experiments (21) on 1-keto-1,2,3,4-tetrahydrophenanthrene demonstrated that it could be converted to 1-phenanthrol by reaction with

---

[2] As pointed out by Stork (90), the conversion of cinchotoxine to cinchoninone by Rabe (70) in 1911 [and later of quinotoxine to quininone (71)] may well represent the earliest example of the bromination of a ketone by an *N*-bromo compound, although it was not formulated as such by Rabe.

N-bromosuccinimide followed by dehydrobromination, but no advantages over the conventional method using bromine seemed apparent.

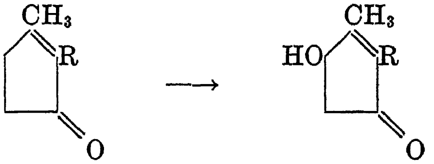
Meystre and Wettstein (54) have examined the action of *N*-bromosuccinimide on α,β-unsaturated steroid ketones, such as testosterone acetate (XXXVIII), where reaction could occur either alpha to the ketone group in position 2 or in the "allyl position" in ring B. The latter was found to be the case; after dehydrobromination 80 per cent of 6-dehydrotestosterone acetate (XXXIX) was obtained by a method of synthesis which was superior to those described earlier for compounds of type XXXIX. It should be noted that in this case, better yields were obtained when the reaction was carried out in the dark with excess *N*-bromosuccinimide for a longer time rather than with strong light, possibly suppressing the competing ketone bromination.



XXXVIII XXXIX

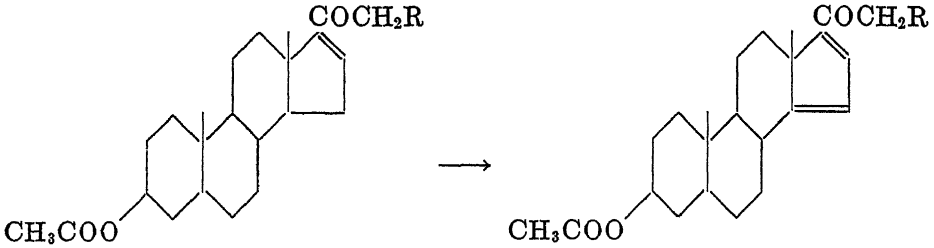
As mentioned before (Sections II,B and II,C), in certain ketones where a reactive double bond or diene structure is present in another part of the same molecule, in the presence of light the methylenic group of the latter can be brominated with *N*-bromosuccinimide without attacking the ketone (see, e.g., compounds XXI and XXXII). Other examples of this specificity are listed in table 3.

The reaction of *N*-bromosuccinimide with α,β-unsaturated ketones has recently been used in the synthesis of dihydrocinerolone (XLIa) (88) and tetrahydropyrethrolone (XLIb) (18) from dihydrocinerone (XLa) and tetrahydropyrethrone (XLb), the intermediate bromo compounds having been converted with carbonate or acetate to the alcohols. The course of the Wohl-Ziegler reaction in this case was used as further evidence for the presently accepted structures of these important insecticides.



XLa: $R = C_4H_9$ XLIa: $R = C_4H_9$
XLb: $R = C_5H_{11}$ XLIb: $R = C_5H_{11}$

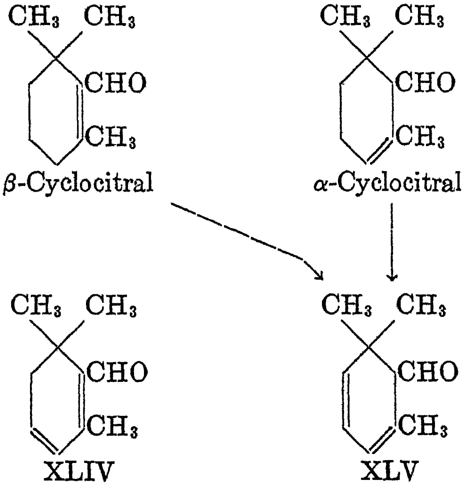
Similar results have been obtained by Plattner and coworkers (66, 67) in certain steroid ketones (XLII), which furnished the doubly unsaturated ring D intermediates (XLIII) of importance for the synthesis of steroid aglucones.



XLII (R = H; OCOCH$_3$) XLIII (R = H; OCOCH$_3$)

With the exception of a preliminary report by Buu-Hoï (12), in which it was claimed[3] that certain ketones of the mesityl oxide type gave the α-bromoketone rather than the allyl bromide, it seems that in general in α,β-unsaturated ketones where bromination of a methylene group alpha to the ketone and alpha to the double bond is possible, the latter reaction occurs.

Aldehydes, in contrast to ketones, have hardly been investigated. Crotonaldehyde and related aldehydes have been reported to lead to decomposition products only (12, 103) when treated with *N*-bromosuccinimide in the usual manner. This could probably be circumvented by using either derivatives such as the acetal (*cf.* 103) or by employing conditions milder than are customary in the Wohl–Ziegler reaction. A very recent publication illustrates this point. Karrer and Ochsner (45a) attempted to prepare safranal (XLIV) from β-cyclocitral and found that the reaction was carried out best by adding *N*-bromosuccinimide in portions while cooling, the reaction being complete in about 5 min. The crude bromination product was dehydrobrominated with collidine to yield an aldehyde isomeric with safranal. Evidence was presented in favor of structure XLV for the product, which was also obtained in the Wohl–Ziegler reaction of α-cyclocitral. It was clear that in the case of β-cyclocitral, migration



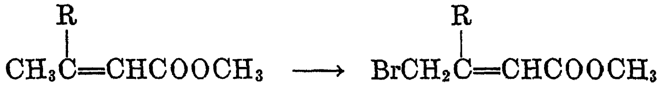
---

[3] No experimental details were given and the evidence presented in favor of the α-bromoketone structure was equivocal, particularly since the possibility of allylic rearrangements was not considered.

of the double bond must have occurred at some stage of the reaction, but the structure of the intermediates was not determined. This example again emphasizes the need for considering the possibility of rearrangements in the Wohl–Ziegler reaction.

E. COMPOUNDS WITH FUNCTIONAL GROUPS (OTHER THAN CARBONYL) ALPHA OR BETA TO A DOUBLE BOND

One of the most important examples of this type was reported first by Ziegler (103)—namely, the allylic bromination of methyl crotonate (XLVIa) and senecioate (XLVIb)—leading to the very important γ-bromo derivatives (XLVII) in excellent yield.

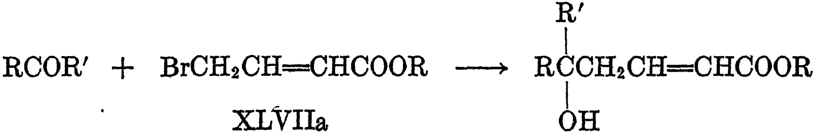


$$CH_3\overset{R}{\overset{|}{C}}=CHCOOCH_3 \longrightarrow BrCH_2\overset{R}{\overset{|}{C}}=CHCOOCH_3$$

XLVIa: $R = H$ XLVIIa: $R = H$

XLVIb: $R = CH_3$ XLVIIb: $R = CH_3$

To appreciate the simplicity of this reaction, one need only examine the many steps which were necessary to prepare these compounds prior to Ziegler's publication (8, 29, 30). As shown by several workers (22, 28, 29, 104), γ-bromocrotonates readily undergo the Reformatsky condensation and the synthesis of these esters through the Wohl–Ziegler reaction has made possible a very useful extension, whereby a four-carbon-atom chain may be introduced at the site of a carbonyl group.



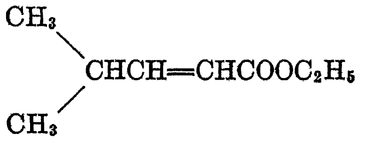
$$RCOR' + \underset{\text{XLVIIa}}{BrCH_2CH=CHCOOR} \longrightarrow R\overset{R'}{\underset{OH}{\overset{|}{\underset{|}{C}}}}CH_2CH=CHCOOR$$

Among the more noteworthy recent applications of the γ-bromocrotonic esters, there should be mentioned the synthesis of compounds related to vitamin A (2, 33, 41, 114), of six-membered rings (16), and of tropinone (45).

The bromination of the next higher homolog, methyl sorbate (XLVIII), also could be accomplished, either in the presence of peroxide (42) or at higher temperature (33) to yield the ϵ-bromo derivative (XLIX), but unfortunately this compound did not undergo the Reformatsky reaction (33, 42).

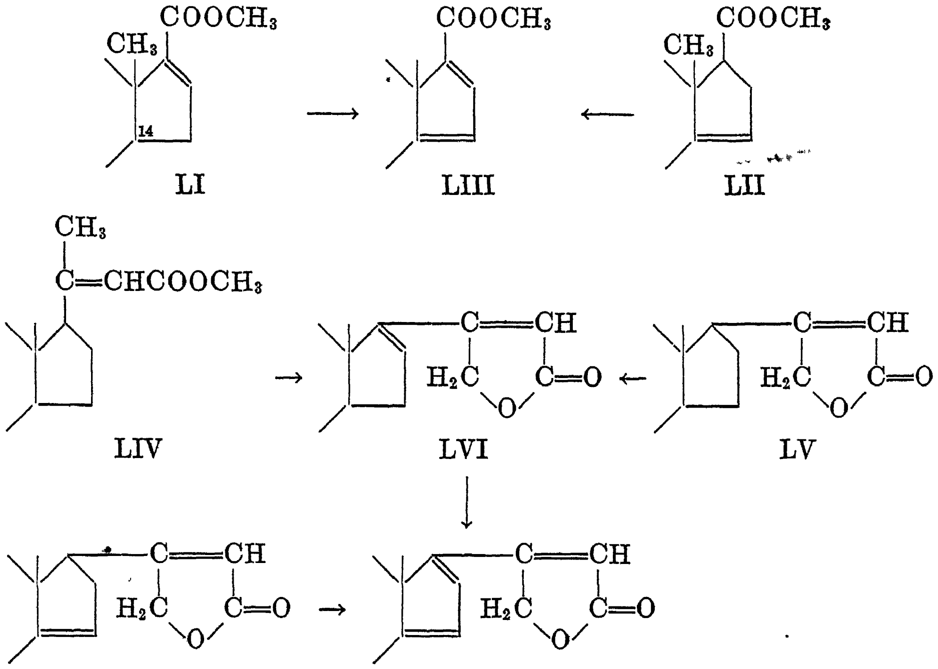
$$\underset{\text{XLVIII}}{CH_3CH=CHCH=CHCOOCH_3} \longrightarrow \underset{\text{XLIX}}{BrCH_2CH=CHCH=CHCOOCH_3}$$

Using peroxide, Schmid and Karrer (86) were able to effect substitution of the tertiary hydrogen of ethyl 4-methyl-2-pentenoate (L), a reaction which was not possible under Ziegler's original conditions.



L

Ruzicka, Plattner, and their coworkers have used the photocatalyzed Wohl-Ziegler reaction in the bromination of α,β-unsaturated esters (LI, LIV) (81, 83), nitriles (68, 84), and lactones (LV, LVI) (64, 82) of the steroid series which has made possible the introduction of a hydroxyl group into position 14 and thus the partial synthesis of compounds of the steroid aglucone type. Starting with the corresponding 14,15-unsaturated derivatives, e.g., LII and LVII, the same type of compound was obtained (64, 65).

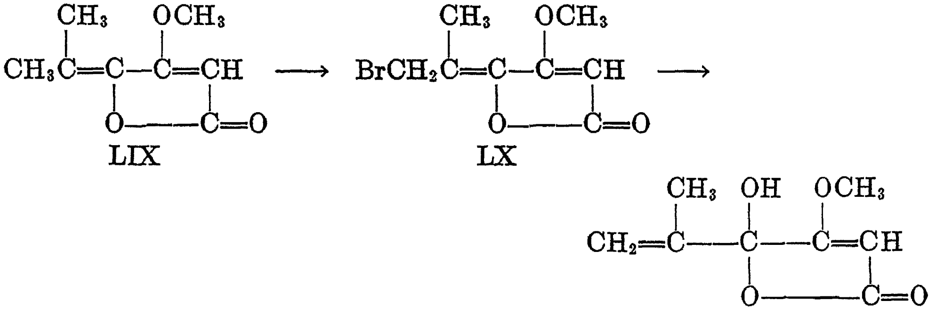


LI LIII LII

LIV LVI LV

LVII LVIII

Recently Raphael (72) treated the unsaturated lactone LIX with N-bromosuccinimide and obtained the ϵ-bromo derivative LX in excellent yield, which in turn could be converted to penicillic acid.



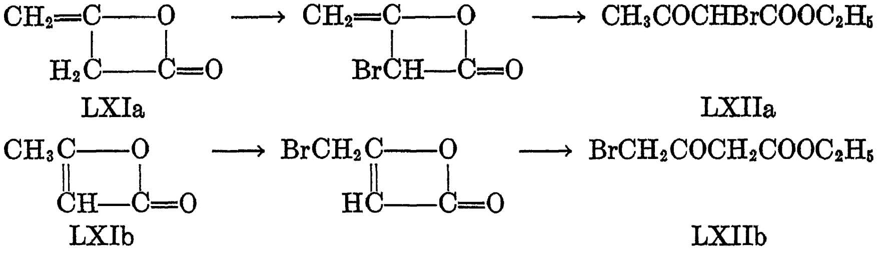
$$\begin{array}{cccccccc} & \mathrm{CH_3} & & & & \mathrm{OCH_3} & & \\ & | & & & & | & & \\ \mathrm{CH_3} & \mathrm{C} & = & \mathrm{C} & — & \mathrm{C} & = & \mathrm{CH} \\ & & & | & & & & | \\ & & & \mathrm{O} & — & — & — & \mathrm{C{=}O} \end{array} \longrightarrow \begin{array}{cccccccc} & \mathrm{CH_3} & & & & \mathrm{OCH_3} & & \\ & | & & & & | & & \\ \mathrm{BrCH_2} & \mathrm{C} & = & \mathrm{C} & — & \mathrm{C} & = & \mathrm{CH} \\ & & & | & & & & | \\ & & & \mathrm{O} & — & — & — & \mathrm{C{=}O} \end{array} \longrightarrow$$

LIX LX

$$\begin{array}{cccccccc} & \mathrm{CH_3} & & \mathrm{OH} & & \mathrm{OCH_3} & & \\ & | & & | & & | & & \\ \mathrm{CH_2{=}} & \mathrm{C} & — & \mathrm{C} & — & \mathrm{C} & = & \mathrm{CH} \\ & & & | & & & & | \\ & & & \mathrm{O} & — & — & — & \mathrm{C{=}O} \end{array}$$

Penicillic acid

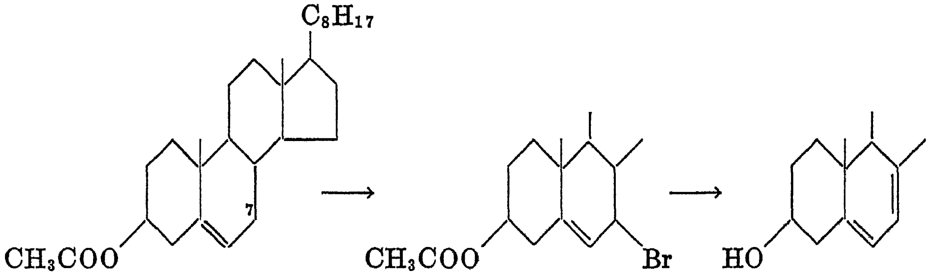
Among the numerous formulations postulated for ketene dimer, the isomeric β-lactone structures (LXIa and LXIb) have been considered seriously on the basis of physicochemical evidence. Blomquist and Baldwin (6a) pointed out that reaction with *N*-bromosuccinimide should lead in each case to a different bromo compound, which on alcoholysis should produce ethyl α-bromoacetoacetate (LXIIa) in the case of the ketene dimer with an exocyclic double bond (LXIa) or the γ-bromo derivative (LXIIb) if the isomeric structure LXIb were the correct one. When tested experimentally, only ethyl α-bromoacetoacetate (LXIIa) was isolated, and this was considered chemical evidence in favor of structure LXIa for ketene dimer. The possibility of an allylic rearrangement should not be discounted however, particularly in view of the resemblance to methylenecyclobutane (37). Furthermore, it has been pointed out recently (120) that ketene dimer probably represents an equilibrium mixture of LXIa and LXIb and it is conceivable that one form (LXIa) reacts preferentially with *N*-bromosuccinimide.



LXIa LXIIa

LXIb LXIIb

Ziegler (103) reported without giving details that cholesterol acetate reacted with *N*-bromosuccinimide. Henbest and coworkers (32) and independently Buisman *et al.* (10) have studied this reaction and reported that bromination occurred in position 7 and that the bromo compound LXIII could be dehydrobrominated to lead to 7-dehydrocholesterol (LXIV) in about 30 per cent over-all yield, thus affording a new and improved synthesis of provitamin D_3. Other cholesterol esters have given similar results (116).



Cholesterol acetate LXIII LXIV

F. AROMATIC HYDROCARBONS

1. Nuclear bromination

Benzene was believed to be unattacked by *N*-bromosuccinimide (11, 25), and it has been used as solvent in the Wohl–Ziegler reaction even in peroxide-catalyzed reactions (see Section IV,B), but Schmid (87) discovered that in the presence of equimolar amounts of certain metal chlorides (aluminum, zinc, and ferric) or sulfuric acid, nuclear bromination of benzene or toluene could be achieved readily. In spite of the large amount of chloride necessary, these compounds are claimed to act as catalysts.

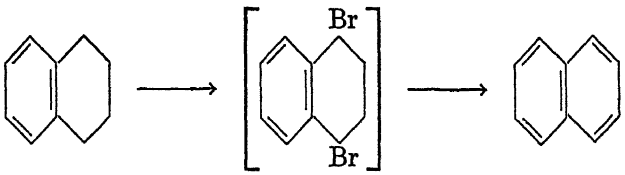
In the case of polynuclear aromatic hydrocarbons (11), catalysts were not necessary, naphthalene and phenanthrene reacting in about 6 hr. to give the 1- and 9-bromo derivatives, respectively; with acenaphthene and anthracene the reaction was complete in a matter of minutes, the corresponding 5- and 9-bromo derivatives being formed.

Already Wohl (99) had observed reaction of *N*-bromoacetamide with anisole, and Buu-Hoï (11) has studied the action of *N*-bromosuccinimide on a wide variety of benzene and naphthalene derivatives, notably ethers. No catalysts were used and the reactions with phenol ethers required several hours for completion, while ethers of α- and β-naphthol reacted in a few minutes.

2. "Side chain" bromination

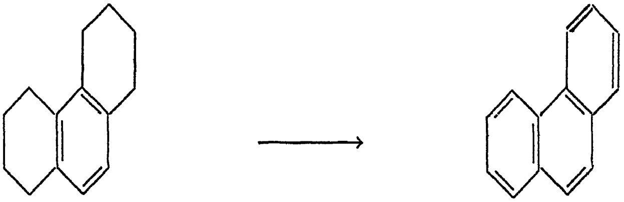
While toluene is not attacked by *N*-bromosuccinimide in the absence of catalysts (11; see, however, 9), Schmid and Karrer (86) demonstrated that benzyl bromide was formed in 64 per cent yield in the presence of peroxide. Thus, in analogy to the behavior of bromine with toluene, substitution can be effected in the nucleus or in the methyl group depending on the conditions employed. In the presence of electronegative groups, "side chain" substitution occurs without catalysts (4, 11). This holds true also for 1- and 2-methylnaphthalenes (11, 13), di- and tri-phenylmethanes (11), fluorene (98), and related compounds. In several dimethylnaphthalenes (13) one methyl group can be brominated selectively. An interesting case is 1-ethylnaphthalene, where "side chain" bromination is observed (13), vinylnaphthalene being obtained in 73 per cent yield in contrast to the closely related acenaphthene, where reaction occurred in the nucleus (11). In the presence of peroxide, the former reaction seemed to predominate (5) and acenaphthylene was isolated. It is quite probable that in a number of the examples studied by Buu-Hoï and coworkers (11, 13), the reaction time could be diminished appreciably and possibly higher yields obtained with the use of catalysts, such as light or peroxide. However, even in the absence of catalysts the yields were quite good (see table 5) and the Wohl–Ziegler reaction is to be preferred in several instances to the classical methods of synthesis for such compounds.

Very recently, Barnes (5) has applied the peroxide-catalyzed Wohl–Ziegler reaction to a number of hydroaromatic hydrocarbons, thereby developing a novel low-temperature method for the dehydrogenation of tetralin types. The reaction was carried out by refluxing the hydrocarbon with the calculated amount of *N*-bromosuccinimide in carbon tetrachloride and dehydrobrominating after the completion of the bromination with acetate. Under those conditions, tetralin (LXV) afforded naphthalene (LXVI) in 74 per cent yield, *sym*-octahydrophenanthrene (LXVII) gave phenanthrene (LXVIII) in 63 per cent yield, and bibenzyl (LXIX) yielded 56 per cent of stilbene (LXX). Other examples of this elegant method are given in table 5.



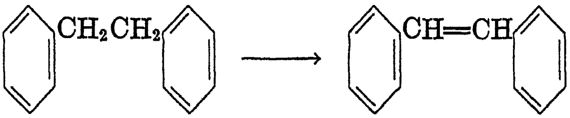
LXV
Tetralin

LXVI
Naphthalene



LXVII
sym-Octahydrophenanthrene

LXVIII
Phenanthrene



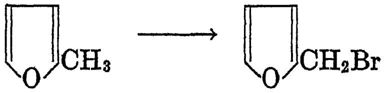
LXIX
Bibenzyl

LXX
Stilbene

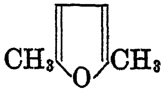
G. HETEROCYCLIC COMPOUNDS

A considerable amount of work needs to be done in investigating the full applicability of the Wohl-Ziegler reaction to heterocyclic compounds. A start in this direction where oxygen is the heteroatom has been made, particularly in France.

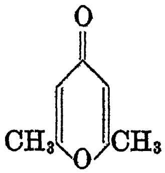
Buu-Hoï and Lecocq (15) observed that 2-methylfuran (LXXI) reacted very vigorously to form 2-bromomethylfuran (LXXII) in excellent yield. With 2,5-dimethylfuran (LXXIII) and 2,6-dimethyl-γ-pyrone (LXXIV) one methyl group could be brominated selectively. In the case of LXXIV, with bromine only nuclear bromination has been observed.



LXXI LXXII

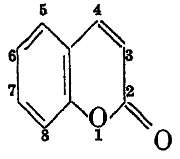


LXXIII

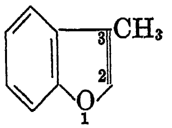


LXXIV

Coumarin (LXXV) derivatives have been studied by Molho and Mentzer (60) and also by Lecocq and Buu-Hoï (47), who noted that a 4-methyl group was never attacked,[4] in contrast to the 3-methyl or ethyl substituents in which case "side chain" bromination was observed. Methyl groups attached to the aromatic ring were substituted with ease.



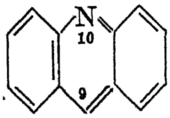
LXXV



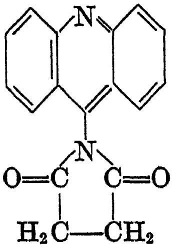
LXXVI

Erlenmeyer and Grubenmann (23) have demonstrated that in the presence of peroxide, reaction with 1 mole of *N*-bromosuccinimide resulted in nuclear substitution of 3-methylbenzofuran (LXXVI) to give the 2-bromo derivative, while 2 moles of *N*-bromosuccinimide led to the 2-bromo-3-bromomethyl compound.

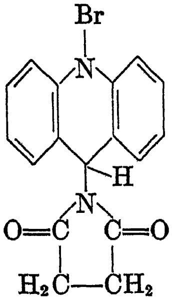
A very detailed study of the reaction of *N*-bromosuccinimide with acridine (LXXVII) has been recorded by Schmid and Leutenegger (87a), who isolated from the complex reaction mixture two monobromoacridines, two dibromoacridines, *N*-(9-acridyl)succinimide (LXXVIII), several brominated derivatives of the latter, acridine hydrobromide, acridone, and three unidentified compounds.



LXXVII
Acridine



LXXVIII



LXXIX

The positions of the bromine atoms were not established, but substitution at position 9 was excluded. To explain the formation of such a variety of products, two reactions of *N*-bromosuccinimide were postulated: (*a*) direct substitution as in other aromatic compounds (see Section II, F) and (*b*) addition of *N*-bromosuccinimide across the 9,10-positions, yielding the hypothetical intermediate LXXIX which loses hydrogen bromide, resulting in the formation of LXXVIII. A combination of both reactions (a and b) would account for the isolation of brominated derivatives of LXXVIII. The hydrogen bromide lost from the hypothetical intermediate LXXIX forms acridine hydrobromide (insoluble in carbon tetrachloride), thus removing some acridine from the reaction mixture, which in turn offers an explanation for the isolation of the dibromo compounds even though only 1 mole of *N*-bromosuccinimide was employed.

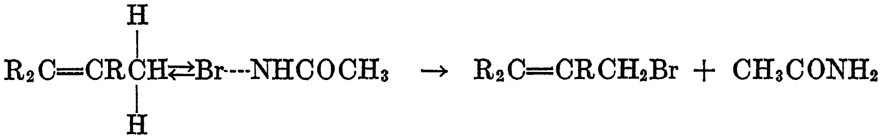
---

[4] The influence of catalysts, however, has not been examined.

Only a few isolated experiments have been recorded with other nitrogen and sulfur heterocyclics, none approaching in thoroughness the above-mentioned work on acridine. "Side chain" bromination has been reported for α- and γ-picolines, quinaldine (11), and 2,5-dimethylthiophene (15). Nuclear bromination of thiophene has been accomplished with both *N*-bromoacetamide (89) and *N*-bromosuccinimide (11). A few other examples are given in table 6.

III. MECHANISM OF THE REACTION

In his first paper Wohl (99) suggested a mechanism for the allylic bromination of olefins with *N*-bromoacetamide in which he postulated the formation of an intermediate complex between the two compounds.



$$R_2C{=}CR\overset{\overset{H}{|}}{\underset{\underset{H}{|}}{C}}H \rightleftarrows Br\text{---}NHCOCH_3 \rightarrow R_2C{=}CRCH_2Br + CH_3CONH_2$$

A difference in the stability of such hypothetical addition complexes was employed by Ziegler and coworkers (103) to account for the observation that the preparation of 3,5-dibromocyclohexene was accomplished readily on treating 3-bromocyclohexene with 1 mole of *N*-bromosuccinimide, but proceeded only with difficulty when 2 moles of the reagent were allowed to react with cyclohexene.

A somewhat similar mechanism in terms of ion-radicals has been used recently by Ettlinger (25), who assumed that after closely approaching each other, the unsaturated compound and *N*-bromoimide underwent electron transfer, resulting in the formation of two unstable ion-radicals "which exchange hydrogen and bromine in a continuous process."

Photocatalysis, peroxide catalysis, and the fact that the point of attack of *N*-bromosuccinimide in olefins usually coincides with that of reagents generally believed to react through free radicals (e.g., benzoyl peroxide, benzenediazonium chloride), all suggest the presence of neutral free radicals (extensive review in reference 25) and such a mechanism is favored at present (34, 35). Already in 1937 Waters (92), in postulating a free-radical mechanism for certain reactions of benzenediazonium chloride, tentatively extended it to positive halogen compounds in general, and its specific applicability to the Wohl-Ziegler reaction has been pointed out recently (93). Bloomfield (7) also favored a neutral, free-radical chain mechanism and depicted the reaction as proceeding through a thermal, homolytic dissociation of *N*-bromosuccinimide (a), followed by abstraction of hydrogen from the methylene group by the free radical (b), and involving chain termination (c) as well as propagation (d).

(a) $(C_4H_4O_2)N{\cdot}Br \rightarrow (C_4H_4O_2)N\cdot + Br\cdot$

(b) $\text{—}CH_2\text{—}C{=}C\text{—} + (C_4H_4O_2)N\cdot \rightarrow \text{—}\dot{C}H\text{—}C{=}C\text{—} + (C_4H_4O_2)NH$

$$\text{(c)}\quad -\dot{C}H{-}C{=}C + Br\cdot \rightarrow -CHBr{-}C{=}C- \;(\text{or } -C{=}C{-}CHBr)$$

$$\text{(d)}\quad -\dot{C}H{-}C{=}C- + (C_4H_4O_2)N{\cdot}Br \rightarrow CHBr{-}C{=}C- \;(\text{or } -C{=}C{-}CHBr) + (C_4H_4O_2)N\cdot$$

This treatment also has been applied to explain the reaction of decalin (5) and of rubber (7) with *N*-bromosuccinimide (see Section II,C). A recent attempt to demonstrate the homolytic dissociation of positive halogen compounds has been recorded by Robertson and Waters (73), who measured the catalytic effect (presumably due to the formation of free radicals) of such substances on the autoöxidation of tetralin. *N*-Bromosuccinimide was found to be a very potent catalyst, in contrast to *N*-bromophthalimide. The analogy of allylic bromination by means of *N*-bromosuccinimide to the free-radical vapor-phase allylic halogenation studied by Rust and Vaughan (78) also has been mentioned (91, 94).

Ettlinger (25) has pointed out that the free radicals formed by thermal dissociation of *N*-bromosuccinimide must possess rather low reactivity, since attack on the solvent (carbon tetrachloride) has not been observed (see also 93) in contrast to the behavior of free radicals produced, for instance, from benzoyl peroxide. Ettlinger (25) reviewed the pertinent literature and also examined the stability of *N*-bromosuccinimide in various solvents, notably dioxane, where decomposition was catalyzed by dioxane peroxide and inhibited by tetrabromohydroquinone. It should be noted that a small amount of *N*-phenylsuccinimide has been isolated (36, 37) in a reaction where benzene was the solvent (see also reference 87a on a similar reaction with acridine).

A report (69) favoring the O—Br rather than N—Br structure for bromophthalimide was written before Ziegler's work (103) became available in Russia.

In conclusion, it can be seen that various investigators have presented indirect evidence to favor a free-radical mechanism for the Wohl–Ziegler reaction with *N*-bromosuccinimide. In the case of *N*-bromophthalimide, it is believed that an ionic mechanism also enters (25), since Ziegler *et al.* (103) observed addition of *N*-bromophthalimide to cyclohexene as well as substitution by halogen. In the case of steroid ethylenes (50) or ketones (19), *N*-bromosuccinimide and *N*-bromophthalimide seem to be equally effective when employed in conjunction with photocatalysis. It should be pointed out that satisfactory mechanisms[5] will have to explain the bromination of olefins in the allyl position, the "side chain bromination" of toluene types, the nuclear bromination of aromatic compounds, and the α-bromination of ketones. Any such mechanism also should account for the amazing reactivity of *N*-bromosuccinimide, the apparently lowered reactivity of *N*-bromophthalimide and, most important, the complete ineffectiveness (103) of *N*-bromoglutarimide, *N*-bromohexahydrophthalimide, and *N*-chlorosuccinimide in the allylic type of reaction. This last observation should be confirmed and repeated, using peroxide and light. It is essential that a sound study of mechanism should be based on comparative data on the effect of variations of experimental conditions (catalysts, temperature, time, etc.) on representative examples of the three major types of reaction, i.e., allylic, nuclear, and ketone bromination. It is unfortunate that some of the speculations on the mechanism of the Wohl-Ziegler reaction are based on isolated examples which are not always comparable from an experimental standpoint.

---

[5] The plural "mechanisms" is used purposely, since it is likely that *N*-bromosuccinimide (and *N*-bromophthalimide) may react by several mechanisms, resulting from homolytic as well as heterolytic dissociation of the reagent. It is highly questionable that the bromination of the methylthiophenes (107), which proceeds in different directions depending on the presence of peroxide, or the addition of bromine to double bonds with *N*-bromosuccinimide (36, 37, 102, 124), as compared to allylic bromination, should all occur by the same mechanism.

IV. Experimental Conditions

A. *N*-BROMOIMIDES

N-Bromosuccinimide is prepared in 75-81 per cent yield by brominating quickly an ice-cold, alkaline solution of succinimide (103). It is desirable to employ *N*-bromosuccinimide of 97 per cent purity or better in the Wohl-Ziegler reaction and for that purpose, the reagent is best recrystallized *quickly* from hot water. Preferably the purity of the product is determined iodometrically (103) rather than relying on the melting point. In the absence of light and moisture, the reagent is stable for many months (25). *N*-Bromosuccinimide is available commercially.

N-Bromophthalimide is synthesized by a nearly identical method (9) from phthalimide.

N-Bromoacetamide can be prepared in 40-55 per cent yield by treating equimolar quantities of acetamide and bromine with a concentrated solution of potassium hydroxide and separating the *N*-bromoacetamide by extraction with hot benzene (6). It has been recommended to store the reagent in the ice box and to use only colorless material melting at 108°C. (99).

B. SOLVENTS

By far the most widely used solvent has been carbon tetrachloride, which was employed almost exclusively by Ziegler in his original studies. In certain cases (7, 24, 25, 36, 37) benzene has added advantages, particularly since *N*-bromosuccinimide is appreciably more soluble in benzene than in carbon tetrachloride. Benzene is not attacked by *N*-bromosuccinimide in the presence of peroxide under ordinary circumstances (87; see, however, 36), but it cannot be used in the presence of catalysts such as aluminum chloride (87; see also Section II,F). Petroleum ether (10, 116) and heptane (37) have been used occasionally, but do not seem to offer any obvious advantages. Although reported only very recently (6a, 121), chloroform has given excellent results particularly in large-scale runs (*cf.* table 4), since it is a more general solvent for organic compounds than carbon tetrachloride and succinimide is soluble in hot chloroform, thus yielding a homogeneous solution. Carbon disulfide (87) gave only poor results in the bromination of toluene. Ethanol has been employed with *N*-bromosuccinimide (27) and *N*-bromoacetamide (101), and ether and acetone have been used with *N*-bromoacetamide (99, 100). Acetic anhydride has been suggested (103) as a possible solvent, but *N*-bromosuccinimide seems to be unstable in it as well as in ethyl acetate, dioxane, and tri-*n*-butylamine (25). *N*-Bromosuccinimide did not attack nitrobenzene in the absence of catalysts (25), but that solvent was useless in the single case tried (bromination of XIX). Ether has been suggested (103) as a possible solvent in the bromination of very reactive methylene groups, but no actual experiments have been described. In many instances (e.g., 11, 33, 89, 103) no solvent is used and the reaction is carried out in an excess of the reactant.

C. MOLAR PROPORTIONS

An excess of olefin was recommended by Ziegler (103) in the bromination of several olefins (table 1), such as cyclohexene to avoid side reactions due to polybromination (see, for instance, the reaction of cyclohexene with 6 moles of *N*-bromosuccinimide (5)). An excess of reactant is used generally in the bromination of aromatic hydrocarbons (11, 87), phenol ethers (11), and related compounds. In steroid brominations, either equimolar amounts or an excess of *N*-bromosuccinimide is employed. Thus, for the bromination of steroid ethylenes and steroid dienes (*cf.* 50, 51, 57) equimolar amounts are suggested and in certain brominations of unsaturated steroid esters and derivatives (68, 83, 84), in contrast to crotonic acid esters (15a, 48, 103), an excess of *N*-bromosuccinimide is used. For steroid ketones equimolar amounts have been employed in conjunction with photocatalysis (19), but an excess may be added without catalysts (54). For dehydrogenations of tetralin types, the calculated amount of *N*-bromosuccinimide is recommended (5). In general, no definite rules can be established and the optimum proportions vary often with the specific example at hand.

D. TEMPERATURE

In most instances, the reactions are carried out at the boiling point of the solvent. In certain unusually reactive compounds, the temperature may be lowered by using a solvent such as ether (103) or by cooling (15, 27, 45a). On the other hand, it has sometimes been found advantageous to operate at higher temperatures. Thus, while the bromination of 1-phenyl-1-propene (103) required about 15 hr. in refluxing carbon tetrachloride solution, the reaction was complete almost instantaneously and without appreciable diminution in yield when carried out at 140°C. A similar observation was made in the bromination of methyl crotonate (103). Reactions at higher temperatures generally are carried out in the absence of a solvent (33, 102, 113). Reactions with *N*-bromoacetamide are performed at room temperature or in an ice bath for prolonged periods of time (99, 100, 101).

E. CATALYSTS

For reactions where photocatalysis is employed, such as in the bromination of steroid ethylenes (50), it has been found useful to combine the sources of heat and light by placing a General Electric reflector drying lamp (250 watts, 115 volts) below the flask. In large batches, several lamps are used to produce refluxing. For peroxide-catalyzed reactions, 5–10 mole per cent of freshly prepared dibenzoyl peroxide has been recommended (86), although sometimes peroxide-containing substances (36) have been used. Mixing the peroxide with *N*-bromosuccinimide in the dry state and using the powdered material subsequently may be advantageous (5). To effect nuclear brominations of aromatic hydrocarbons, such as benzene or toluene, 1 mole of aluminum, zinc, or ferric chloride or sulfuric acid has to be used, since smaller amounts give poor results (87).

F. GENERAL PROCEDURE

Dry reagents are essential to avoid hydrolysis of the *N*-bromoimide. In general, the reactant is dissolved in carbon tetrachloride or another suitable solvent, *N*-bromosuccinimide or *N*-bromophthalimide is added, and the mixture is refluxed. The disappearance of the insoluble *N*-bromoimide on the bottom with the simultaneous formation of the insoluble imide floating on top indicates the completion of the reaction. This can be confirmed by testing for the absence of bromine (starch–iodide test). Quite often, e.g., in the case of ketones (19), a color develops in the beginning which disappears suddenly when the reaction is complete. This has also been observed in other instances (5, 86). After the completion of the reaction, the insoluble imide is filtered, washed with solvent, and the filtrate is worked up in a suitable manner (removal of solvent, followed by crystallization, distillation, etc.) to isolate the product. The proper conditions will have to be chosen for each particular case, taking into consideration the remarks made in Section III, A to E. In general the reaction is carried out first without catalysts and if unsuccessful (owing to incomplete reaction or other reasons), peroxide or light or both (43) can be employed as catalysts. A combination of several variables may be considered to achieve selectivity or minimize side reactions (*cf.* 54). The wide variety of experimental conditions which can be used are rather obvious and represent a particularly attractive feature of the Wohl–Ziegler reaction.

In many instances, the resulting bromo compound is unstable and loses the elements of hydrogen bromide spontaneously on longer refluxing (*cf.* 50, 51, 53). In those cases where loss of hydrogen bromide is only partial, the succinimide is filtered at the end of the reaction (negative potassium iodide test, absence of heavy precipitate on the bottom), the solvent is removed and a base is added to complete dehydrobromination; potassium or sodium acetate (5, 38), sodium carbonate (13), dimethylaniline (49, 51, 56), pyridine (*cf.* 19, 64, 82), collidine (10, 21, 45a, 54), alumina (81), and similar reagents have been used. It should be noted that in particularly unstable bromo compounds, where dehydrobromination occurs before bromination is complete, hydrogen bromide can liberate free bromine from *N*-bromosuccinimide and give rise to side reactions (97).

V. CONCLUSION

It is evident that although a considerable amount of ground has been covered, much work remains to be done to determine the full scope of the Wohl–Ziegler reaction. The fairly recent introduction of catalysts—light, peroxide, metal chlorides—necessitates the repetition of many of the earlier experiments, particularly unsuccessful ones, in which catalysts have not been used, in order to demonstrate the feasibility of the Wohl–Ziegler reaction in those cases.

A great deal of work still is to be done in the field of heterocyclics, where promising results may be expected. With one questionable exception (100), acetylenic compounds have not yet been examined. More definite evidence also will be needed to put the reaction mechanism on a strong footing.

VI. TABLES

Practically all compounds which have been investigated in the Wohl–Ziegler reaction up to January 1, 1948 are given in tables 1 to 7. A few arbitrary classifications have been made; for instance, XXI is given under monoölefins rather than polyolefins, since the reaction only involves the isolated double bond in the side chain, but the compound is also classified under carbonyl compounds. Under reaction conditions, the time given denotes the period at reflux temperature, unless stated otherwise; dehydrobrominating agents are usually not specified.

The author is indebted to Dr. David R. Howton, California Institute of Technology, Dr. Roderick A. Barnes, Rutgers University, Dr. H. B. Henbest, Imperial College of Science and Technology, Dr. John D. Roberts, Massachusetts Institute of Technology, and Dr. Karl Dittmer, University of Colorado, for furnishing unpublished material, and to Dr. Gilbert Stork, Harvard University, for stimulating correspondence. The helpful suggestions of Dr. C. R. Scholz of this laboratory are gratefully acknowledged.

VII. REFERENCES

(1) ALDER, K., PASCHER, F., AND SCHMITZ, A.: Ber. **76**, 27 (1943).
(2) AHRENS, J. F., AND VAN DORP, D. A.: Nature **157**, 190 (1946): Rec. trav. chim. **65**, 338 (1946).
(3) BAKER, W.: J. Chem. Soc. **1945**, 258.
(4) BARNES, R. A., AND GORDON, L.: To be published.
(5) BARNES, R. A.: J. Am. Chem. Soc. **70**, 145 (1948).
(6) BEHREND, R., AND SCHREIBER, H.: Ann. **318**, 371 (1901).
(6a) BLOMQUIST, A. T., AND BALDWIN, F. H.: J. Am. Chem. Soc. **70**, 29 (1948).
(7) BLOOMFIELD, G. F.: J. Chem. Soc. **1944**, 114.
(8) BRAUN, G.: J. Am. Chem. Soc. **52**, 3167 (1930).
(9) BREDT, J., AND HOF, H.: Ber. **33**, 21 (1900).
(10) BUISMAN, J. A. K., STEVENS, W., AND VLIET, J.: Rec. trav. chim. **66**, 83 (1947).
(11) BUU-HOÏ: Ann. **556**, 1 (1944).
(12) BUU-HOÏ: Experientia **2**, 310 (1946).
(13) BUU-HOÏ, AND LECOCQ, J.: J. Chem. Soc. **1946**, 830.
(14) BUU-HOÏ, HIONG-KI-WEI, LECOMTE, J., AND ROYER, R.: Bull. soc. chim. France **1946**, 148.
(15) BUU-HOÏ AND LECOCQ, J.: Compt. rend. **222**, 1441 (1946).
(15a) CAMPBELL, N. R., AND HUNT, J. H.: J. Chem. Soc. **1947**, 1176.
(16) COOK, J. W., AND SCHOENTAL, R.: J. Chem. Soc. **1945**, 288.
ROSS, W. C. J.: J. Chem. Soc. **1947**, 1367.
BACHMANN, W. E., AND WENDLER, N. L.: J. Am. Chem. Soc. **68**, 2580 (1946).
STORK, G.: J. Am. Chem. Soc. **69**, 2936 (1947).

TABLE 1

Wohl-Ziegler reaction of monoölefins

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Aliphatic and alicyclic olefins:*			
Propylene	NBA,* ether, 19 days, room temperature	29% dibromo derivative	(100)
2-Methyl-2-butene	2NBA, acetone, cold	50% dibromo derivative	(99)
	1/2NBS, CCl_4, 16 hr.	40% monobromoamylene	(103)
2,3-Dimethyl-2-butene	NBA, ether, 12 hr.	16% 1-bromo-2,3-dimethyl-2-butene	(99)
2-Bromo-3-methyl-2-butene	NBA, acetone, 24 hr., room temperature	13–22% dibromo derivative	(99)
2-Methyl-2-hexene	1/2NBS, CCl_4, 10 min.	40% 4(?)-bromo-2-methyl-2-hexene	(103)
2-Octene	1/3NBS, CCl_4, 1 hr.	70% monobromoöctene	(103)
Diisobutylene	1/3NBS, CCl_4, 5 hr.	68% monobromoisobutylene	(103)
4-Nonene	NBS, CCl_4, 40 min.	65% monobromononene	(103)
1-Dodecylene	1/2NBS, CCl_4, 5 min.	77% monobromododecylene	(103)
	2NBS, CCl_4, 32 min.	33% 1,4(?)-dibromo-2-dodecylene	(103)
3-Bromo-1-dodecylene	NBS, 4 hr.	40% 1,4(?)-dibromo-2-dodecylene	(103)
Ethyl undecylate	1/3NBS, CCl_4, 30 min.	46% monobromo derivative	(103)
Methyl oleate	NBS, CCl_4, 40 min.	Quantitative yield of monobromo derivative	(103)
Cyclobutene	NBS, C_6H_6, 6 hr., peroxide	67% 1,2-dibromocyclobutane, trace 3-bromocyclobutene	(37)
Methylenecyclobutane	NBS, C_6H_6, 6 hr., peroxide	13.5% 2-bromo-1-methylenecyclobutane, 1.5 % 1-bromomethyl-1-cyclobutene, 57% methylenecyclobutane dibromide, 15% *N*-phenylsuccinimide	(37)
1-Methylcyclopentene	"Ziegler's conditions"	Unstable bromo derivative	(61)
1-Chlorocyclopentene	"Ziegler's conditions"	3-Bromo-1-chloro-1-cyclopentene	(61)
Cyclohexene	NBP, CCl_4, 1 hr.	50% 3-bromo-1-cyclohexene, 21% *N*-(2-bromocyclohexyl)phthalimide	(103)
	1/5NBS, (CCl_4), 20 min.	82–87% 3-bromocyclohexene	(103)
	NBS, C_6H_6, 32 min., peroxide	50% 3-bromo-1-cyclohexene, 6.4% 1,2-dibromocyclohexane, 2% 3,6-dibromo-1-cyclohexene, 1% *N*-phenylsuccinimide	(36, 110)
	6NBS, CCl_4, 12 hr., per-	58% *m*- and *p*-dibromo-	(5)

TABLE 1—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
1-Methyl-1-cyclohexene	"Ziegler's conditions"	Chiefly 6-bromo-1-methyl-1-cyclohexene, trace of 3-bromo isomer	(61)
1-Methyl-2-cyclohexene	"Ziegler's conditions"	4-Bromo-1-methyl-2-cyclohexene	(61)
1-Methyl-3-cyclohexene	"Ziegler's conditions"	5-Bromo-1-methyl-3-cyclohexene	(61)
Methylenecyclohexane	"Ziegler's conditions" (long heating)	2-Bromo-1-methylenecyclohexane, polybromo compounds	(61)
1-Ethylcyclohexene	"Ziegler's conditions"	6-Bromo-1-ethylcyclohexene	(61)
1,3-Dimethyl-3-cyclohexene	"Ziegler's conditions"	2-Bromo-1,3-dimethyl-3-cyclohexene	(61)
1-Chlorocyclohexene	"Ziegler's conditions"	3-Bromo-1-chloro-1-cyclohexene	(61)
3-Bromo-1-cyclohexene	1/3NBS, CCl_4, 1 min.	31% 3,6-dibromo-1-cyclohexene	(103)
Cyclooöctene	NBS	1,3-Cyclooöctadiene	(103)
9,10-Octalin	4NBS, CCl_4, peroxide	30% *x*-tetrabromooöctalin	(5)
Styrene	NBS	No reaction	(46)
α-Methylstyrene	NBS	Reacts	(103)
1-Phenyl-1-propene	1/2NBS, CCl_4, 15.5 hr.	75% cinnamyl bromide; 67% when carried out at 140°C. (instantaneous reaction)	(103)
1,1-Diphenyl-1-propene	NBS, CCl_4, 18 hr.	86% γ,γ-diphenylallyl bromide	(103)
1,1-Diphenyl-1-butene	NBS, CCl_4, 95 min.	3-Bromo-1,1-diphenyl-1-butene	(103)
1, 1-Diphenyl-4-methyl-1-pentene	NBS, CCl_4, light, then dehydrobrominate	1,1-Diphenyl-4-methyl-1, 3-pentadiene	(58a)
Diethylstilbestrol dipropionate	2NBS, CCl_4, 30 min.	64% 3,4-bis(*p*-propionoxyphenyl)-2,5-dibromo-3-hexene	(111)
(*2*) *Isoprenoids:*			
α-Pinene	2/5NBS, CCl_4, 1 hr.	60% monobromopinene (XIIa)	(14, 103)
Camphene	1/2NBS, CCl_4, 24 hr., peroxide, light	24% ω-bromocamphene, 9% alkyl bromide, 7% allyl bromide	(124)

TABLE 1—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Norbornylene	1/2NBS, 2.5 hr., peroxide, light (21% yield in presence of HBr or absence of catalyst)	41% 7-bromonorbornylene	(124)
Cedrene	NBS, CCl_4, 10 min.	(Bromocedrene) oxidized in 35% yield to norcedrenedicarboxylic acid	(63)
$\Delta^{6,7}$-23-Nor-α-amyrene	NBS (70%), CCl_4, 4 hr.	65% $\Delta^{6,7;8,9}$-23-nor-α-amyradiene, 10% hexabromo derivative	(80)
$\Delta^{6,7}$-23-Nor-2-keto-α-amyrene	NBS, CCl_4, 4 hr., $BaCO_3$	$\Delta^{6,7;8,9}$-23-Nor-2-keto-α-amyradiene	(80)
β-Amyrin acetate	NBS (65%), CCl_4, 2 hr.	80% β-amyratrienol acetate (XV)	(79)
β-Amyrin benzoate	NBS, CCl_4, 3 hr.	2% β-amyratrienol benzoate, 9% bromo-β-amyratrienol benzoate	(62)
α-Amyrin acetate	NBS (65%), CCl_4, 2 hr.	80% α-amyradienol acetate	(79)
Methyl acetylursolate	NBS (65%), CCl_4, 2 hr.	70–75% methyl acetyldehydroursolate	(79)
(3) *Steroids:*			
Δ^{23}-24,24-Diphenylallocholene	NBS, CCl_4, 12 min., light, then dehydrobrominate	21% pure diene; 44% over-all to 17-methyl ketone	(51)
Δ^{23}-3(β)-Acetoxy-24,24-diphenylallocholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	70% diene	(52, 97)
Δ^{23}-3(α)-Acetoxy-24,24-diphenylcholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	*ca.* 50% diene	(52)
$\Delta^{4;23}$-3-Keto-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light, then dehydrobrominate	$\Delta^{4;20;23}$-3-Keto-24,24-diphenylcholatriene (XXII)	(56)
Δ^{23}-3(α),6(β)-Diacetoxy-24,24-diphenylcholene	NBS, CCl_4, 15 min., light, then dehydrobrominate	(Crude diene) 37% over-all to 17-methyl ketone (crude)	(59)
Δ^{23}-3(α),12(α)-Diacetoxy-24,24-diphenylcholene	NBS, C_6H_6, 2 hr., then dehydrobrominate	(Crude diene) 23% over-all to 17-methyl ketone	(24)
	NBS, CCl_4, 10 min., then dehydrobrominate	(Crude diene), 25% over-all to 17-methyl ketone	(49)
	NBS, CCl_4, 15 min., light, then dehydro-	82% diene (same with NBP)	(50)

TABLE 1—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Δ^{23}-3(α),12(α)-Diacetoxy-23,23-diphenylnorcholene..........	NBS, CCl_4, light	No reaction	(50)
Δ^{23}-3(β)-Acetoxy-5-chloro-24,24-diphenylcholene...	NBS, CCl_4, 20 min., light, then dehydrobrominate	56% diene	(53)
Δ^{23}-3(α)-Acetoxy-11-keto-24,24-diphenylcholene.............	NBS, CCl_4, 15 min., light, then dehydrobrominate	*ca.* 60% diene	(96)
Δ^{23}-3(α),7(α),12(α)-Triacetoxy-24,24-diphenylcholene.......	NBS, CCl_4, 15 min., light, then dehydrobrominate	Quantitative yield of crude diene; 39% overall to 17-methyl ketone	(51)

* NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.
NBP = *N*-bromophthalimide.

TABLE 2

Wohl–Ziegler reaction of polyolefins

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Non-conjugated:*			
1,5-Hexadiene..........	4/5NBS,* CCl_4, 8 hr., light, peroxide	45% 3-bromo-1,5-hexadiene	(43, 44, 117)
3-Bromo-1,5-hexadiene.	NBS, CCl_4, 6 hr., light, peroxide	52% 1,6-dibromo-2,4-hexadiene	(43, 44)
1,5-Cycloöctadiene.....	NBS, CCl_4, 1 hr, peroxide	57% monobromo derivative	(17)
	2NBS, CCl_4, 1 hr, peroxide, then $(CH_3)_2NH$	34% 5,8-bis(dimethylamino)-1,3-cycloöctadiene	(17)
Dihydromyrcene.......	NBS, CCl_4, N_2	Monobromo derivative	(7)
Rubber................	NBS, $C_6H_6(CCl_4)$, 1/2 hr.	Bromo-rubber	(7)
2,9-Dimethyl-2,8-decadiene................	2NBS, CCl_4, 1/2 hr.	Dibromo derivative	(103)
Lycopene.............	2NBS, CCl_4, 2 hr.	20% dehydrolycopene	(39)
(*2*) *Conjugated:*			
1,3-Cyclohexadiene....	1/3NBS, CCl_4, 6 hr.	No definite product	(103)
1,3(?)-Dodecadiene.....	2/3NBS, CCl_4, 10 hr.	28% (crude) bromododecadiene	(103)
Methyl abietate........	NBS, CCl_4, 3 hr., $BaCO_3$, then CH_3COONa	32% dehydroabietic acid	(38)

TABLE 2—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
1,1,4a-Trimethyl-7-isopropyl-1,2,3,4,4a,5,6,9,10,10a-decahydrophenanthrene	NBS, CCl_4, 1 hr., $BaCO_3$, then CH_3COONa	23% dehydroabietane	(38)
β-Amyradienol-II acetate	NBS, CCl_4, 3 hr.	β-Amyratrienol acetate	(62)
β-Amyradienol-I acetate	NBS (80%), CCl_4, 2 hr.	β-Amyratrienol acetate	(62)
$\Delta^{4;20;23}$-3-Keto-24,24-diphenylcholatriene	NBS, CCl_4, 10 min., light	$\Delta^{4;20;23}$-3-Keto-21-bromo-24,24-diphenylcholatriene	(58)
$\Delta^{20;23}$-3,11-Diketo-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	62% $\Delta^{20;23}$-3,11-diketo-21-bromo-24,24-diphenylcholadiene	(96)
$\Delta^{20;23}$-3-Keto-12(α)-acetoxy-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	69% $\Delta^{20;23}$-3-keto-12(α)-acetoxy-21-bromo-24,24-diphenylcholadiene	(57)
$\Delta^{20;23}$-3(α),12(α)-Diacetoxy-24,24-diphenylcholadiene	NBS, CCl_4, 10 min., light (1 hr. without light)	71% $\Delta^{20;23}$-3(α),12(α)-diacetoxy-21-bromo-24,24-diphenylcholadiene	(57)
$\Delta^{20;23}$-3(β)-Acetoxy-5-chloro-24,24-diphenylcholadiene	NBS, CCl_4, 20 min., light	74% $\Delta^{20;23}$-3(β)-acetoxy-5-chloro-21-bromo-24,24-diphenylcholadiene	(58)

* NBS = *N*-bromosuccinimide.

TABLE 3

Wohl–Ziegler reaction of carbonyl compounds

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Non-conjugated:*			
Ethyl acetoacetate	NBP* or NBA, ether, cold	45% ethyl α-bromoacetoacetate	(99, 100)
2-Methyl-2-hepten-6-one	NBS, CCl_4	Bromination alpha to keto group	(12)
Cyclohexanone	NBS, CCl_4, 40 min.	2-Bromocyclohexanone	(86)
Tetrahydro-γ-pyrone	NBS, CCl_4, 25 min., light	50% 3,5-dibromo derivative	(125)

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
α-Cyclocitral	NBS, CCl_4, 5 min., 30°C., then dehydrobrominate	2,2,6-Trimethyl-3,5-cyclohexadien-1-aldehyde	(45a)
Methyl 2-keto-3-phenylhydrazono-8-octanecarboxylate	NBS, CCl_4, few minutes	Methyl 1-bromo-2-keto-3-phenylhydrazono-8-octanecarboxylate	(86)
	2NBS, CCl_4, 20 min.	53% methyl 1-bromo-2-keto-3-(*p*-bromophenylhydrazono)-8-octanecarboxylate, 19% 3-bromo isomer	(86)
1-Keto-1,2,3,4-tetrahydrophenanthrene	NBS, CCl_4, 4 min., light, then dehydrobrominate (collidine)	57% 1-phenanthrol	(21)
Cholestan-3-one	NBS or NBP, CCl_4, 1 min., light (30 min., no light)	66% 2-bromocholestanone	(19)
2-Bromocholestan-3-one	NBS, CCl_4, 1 min., light	52% (crude) 2,2-dibromocholestanone	(19)
Dihydrotestosterone hexahydrobenzoate	NBS, CCl_4, 4 min., light	50% 2-bromo derivative	(19)
Methyl 3-ketoalloetiocholanate	NBS, CCl_4, 2 min., light	54% 2-bromo derivative	(19)
Coprostan-3-one	NBP, CCl_4, light	33% 4-bromocoprostanone	(19)
Methyl 3-keto-12-hydroxycholanate	NBS, CCl_4, 4 min., light, then dehydrobrominate	30% Δ^4-3-keto-12-hydroxycholenate	(19)
$\Delta^{6,7}$-23-Nor-2-keto-α-amyrene	NBS, CCl_4, 4 hr., $BaCO_3$	Bromination α to double bond (see table 1)	(80)
Δ^{23}-3(α)-Acetoxy-11-keto-24,24-diphenylcholene	NBS, CCl_4, 15 min., light	Bromination in position 22 (see table 1)	(96)
$\Delta^{20;23}$-3,11-Diketo-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	Bromination in position 21 (see table 2)	(96)
(2) *α,β-Conjugated:*			
Crotonaldehyde	NBS	Black decomposition product	(12, 103)
Crotonaldehyde diethylacetal	NBS	Reacts	(103)
3-Penten-2-one	NBS, CCl_4	1-Bromo-3-penten-2-one	(12)
4-Methyl-3-penten-2-one	NBS, CCl_4	1-Bromo-4-methyl-3-	(12)

TABLE 3—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Dihydrocinerone (XLa)	NBS, CCl_4, 18 hr.	2-Butyl-3-methyl-4-bromo-2-cyclopenten-1-one	(88)
Tetrahydropyrethrone (XLb)	NBS, CCl_4, 1/2 hr.	67% 2-amyl-3-methyl-4-bromo-2-cyclopenten-1-one	(18)
2,5-Diphenyl-4-cyclopentene-1,3-dione	NBS, CCl_4, 48 hr.	70% 2-bromo-2,5-diphenyl-4-cyclopentene-1,3-dione	(76)
Triphenylcyclopentenone	NBS, CCl_4, 14 hr.	Monobromo derivative	(77)
β-Cyclocitral	NBS, CCl_4, 5 min., 30°C., then dehydrobrominate	15–20% 2,2,6-trimethyl-3,5-cyclohexadien-1-aldehyde	(45a)
Progesterone	3NBS, CCl_4, 1½ hr., dark	6-Bromoprogesterone	(54)
Testosterone acetate	3NBS, CCl_4, 5 hr., dark, then dehydrobrominate	80% 6-dehydrotestosterone acetate	(54)
$\Delta^{4;23}$-3-Keto-24,24-diphenylcholadiene	NBS, CCl_4, 15 min., light	Bromination in position 22 (table 1)	(56)
$\Delta^{4;20;23}$-3-Keto-24,24-diphenylcholatriene	NBS, CCl_4, 10 min., light	Bromination in position 21 (table 2)	(58)
Δ^{16}-3(β)-Acetoxy-20-keto-5-allopregnene	NBS, CCl_4, 15 min., light, then dehydrobrominate	55% $\Delta^{14;16}$-3(β)-acetoxy-20-keto-5-allopregnadiene	(66)
Δ^{16}-3(β),21-Diacetoxy-20-keto-5-allopregnene	NBS, CCl_4, 1/2 hr., light, then dehydrobrominate	49% $\Delta^{14;16}$-3(β), 21-diacetoxy-20-keto-5-allopregnadiene (35% with peroxide)	(67)
β-Ionone	NBS, CCl_4, then dehydrobrominate	Dehydro-β-ionone	(115)
1,3-Diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone	NBS, CCl_4, 1 hr.	85–92% 1,3-diacetyl-4-bromomethyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone	(108, 109)
1,3-Dipropionyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone	NBS, CCl_4, 1 hr.	53% 4-bromomethyl derivative	(109)

* NBP = *N*-bromophthalimide.
NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.

TABLE 4

Wohl-Ziegler reaction with compounds possessing functional groups (other than carbonyl) alpha or beta to a double bond

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(1) Functional group alpha to double bond:			
Allyl alcohol...........	NBA,* ether, 4 days, cold	Mono- and di-bromo derivatives	(100)
Crotonic acid.........	2NBA, acetone, 40 hr., cold	Monobromo derivative	(100)
Methyl crotonate......	1/2NBS, CCl_4, 13 hr.	86% methyl γ-bromocrotonate	(103)
Methyl crotonate (2¾ moles)..............	2NBS, 300 cc. $CHCl_3$, 5 min. (peroxide)	80% methyl γ-bromocrotonate	(121)
Ethyl crotonate........	1/2NBS, CCl_4, 6 hr. (peroxide)	82% ethyl γ-bromocrotonate	(22, 48)
Methyl senecioate......	1/4NBS, 8 min.	60–80% methyl γ-bromosenecioate	(103)
Diethyl mesaconate....	2/3NBS, CCl_4, 1 hr., peroxide	68% diethyl γ-bromomesaconate	(15a)
Ethyl β-ethoxycrotonate..................	NBA, ether, 2 days, cold	Ethyl γ-bromo-β-ethoxycrotonate	(100)
1-Ethoxybutadiene.....	5NBS, ethanol, 2 hr., room temperature	64% γ-bromocrotonaldehyde diethyl acetal	(27)
Methyl sorbate.........	1/4NBS, stirred 120°C.	65% methyl ϵ-bromosorbate	(33)
	NBS, CCl_4, 20 min., 110°C., peroxide	39% crude, 6% pure	(42)
Ethyl 4-methyl-2-pentenoate.............	NBS, CCl_4, several hours, peroxide	67% ethyl 4-bromo-4-methyl-2-pentenoate	(86)
3-Acetoxycyclohexene..	1/2NBS, CCl_4, 30 min.	58% 3-acetoxy-6-bromocyclohexene	(103)
3-Ethoxycyclohexene...	NBS	Mixture of monobromo compounds	(103)
Isocantharic acid No. 2 methyl ester.........	NBS, 6 hr., 135°C.	36% *x*-(4,5?)-bromoisocantharic acid methyl ester	(102)
β-Cyclogeranic acid....	NBA	3-Bromo-β-cyclogeranic acid	(95)
Ethyl β-ethoxycinnamate.......	NBA, ether, 5 days, cold	76% ethyl α-bromo-β-ethoxycinnamate	(100)
3-Methoxy-4-hydroxy-5-methyl-2,4-hexadienic acid lactone.....	NBS, CCl_4, peroxide	6-Bromo-3-methoxy-4-hydroxy-5-methyl-2,4-hexadienic acid lactone (good yield)	(72)

TABLE 4—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Methyl Δ^{16}-3(β)-acetoxyalloetiocholenate	1.13NBS, CCl$_4$, 10 min., light, then dehydrobrominate	77% methyl $\Delta^{14;16}$-3(β)-acetoxyalloetiocholadienate (50% without light)	(83)
Methyl $\Delta^{20;22}$-3(β)-acetoxyallonorcholenate.	NBS, CCl$_4$, 20 hr., then alumina	Less than 10% β'-[Δ^{16}-3(β)-acetoxyalloetiocholenyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	(81)
Δ^{16}-3(β)-Acetoxy-5-alloetiocholenenitrile	1.3NBS, CCl$_4$, 20 min., light, then dehydrobrominate	77% $\Delta^{14;16}$-3(β)-acetoxy-5-alloetiocholadienenitrile	(68)
Δ^{16}-3(β)-Acetoxyetiocholenenitrile	1.25NBS, CCl$_4$, 12 min., light, then dehydrobrominate	81% $\Delta^{14;16}$-3(β)-acetoxyetiocholadienenitrile	(84)
β'-[3(β)-Acetoxyalloetiocholanyl-(17)]-$\Delta^{\alpha'\beta'}$ butenolide.	NBS, CCl$_4$, 20 min., light, then dehydrobrominate	63% β'-[Δ^{16}-3(β)-acetoxyalloetiocholenyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	(82)
β'-[$\Delta^{16,17}$-3(β)-Acetoxyalloetiocholenyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	NBS, CCl$_4$, 2 hr., light, then dehydrobrominate	13% β'-[$\Delta^{14,15;16,17}$-3(β)-acetoxyalloetiocholadienyl-(17)]-$\Delta^{\alpha'\beta'}$-butenolide	(64)
β-Anhydrodigoxigenin diacetate	NBS, CCl$_4$, 2 hr., light, then dehydrobrominate	58% anhydro-16,17-dehydrodigoxigenin diacetate	(64)
Δ^{16}-3(β)-Acetoxy-5,6-dibromoetiocholenenitrile	NBS, CCl$_4$, 8 min., light, then KI	80% $\Delta^{5;16}$-3(β)-acetoxy-15-bromoetiocholadienenitrile	(123)
(*2*) *Functional group beta to double bond:*			
Ketene dimer (LXIa)	NBS, CHCl$_3$, distill solvent, then ethanol + trimethylamine	43% ethyl α-bromoacetoacetate	(6a)
1,2-Dimethyl-1,2,3,6-tetrahydrophthalic anhydride	NBS, CCl$_4$, 5 hr.	Quantitative (crude) 6-bromo-1,2-dimethyl-1,2,3,6-tetrahydrophthalic anhydride	(102)

TABLE 4—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Methyl acetyl-β-boswellinate........	NBS (70%), CCl_4, 3 hr.	Methyl $\Delta^{6,7;8,9}$-2-acetoxy-α-amyradiene-23-carboxylate	(80)
Methyl Δ^{14}-3(β)-acetoxy-5-alloetiocholenate...........	NBS, CCl_4, light, then dehydrobrominate	69% methyl $\Delta^{14;16}$-3(β)-acetoxy-5-alloetiocholadienate	(65)
Methyl Δ^{14}-3(β)-acetoxy-17-iso-5-alloetiocholenate.....	NBS, CCl_4, light, then dehydrobrominate	65% methyl $\Delta^{14;16}$-3(β)-acetoxy-5-alloetiocholadienate	(65)
Cholesterol acetate....	NBS, petroleum ether, 7 min., light, then dehydrobrominate	29% 7-dehydrocholesterol acetate (bromo compound isolated)	(10, 32, 103)
Cholesterol benzoate...	NBS, petroleum ether (80–100°C.)	35% 7(β)-bromo derivative	(116)
Cholesteryl chloride....	NBS, petroleum ether	50% 7(β)-bromo derivative	(116)
Cholesteryl bromide....	NBS, petroleum ether	50% 7(β)-bromo derivative	(116)

* NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.

TABLE 5

Wohl–Ziegler reaction with aromatic hydrocarbons

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Nuclear bromination:*			
Benzene......	NBS,* 1 hr., 95°C.	No reaction	(11, 25)
	NBS, 4–16 hr., depending on catalyst ($AlCl_3$, H_2SO_4, etc.)	41–67% bromobenzene, small amount of di- and tetra-bromobenzenes	(87)
Toluene...	NBS, 1½–7 hr., depending on catalyst	21–71% *p*-bromotoluene, some polybromotoluene	(87)
1-Methyl-3,4-dihydronaphthalene..........	NBS with difficulty	Nuclear bromination	(122)
Naphthalene...........	1/3NBS, CCl_4, 6 hr.	77% α-bromonaphthalene	(11)
Biphenyl....	NBS, CCl_4, $FeCl_3$, several days	4-Bromobiphenyl	(105)
Acenaphthene...... . .	1/2NBS, CCl_4, 10 min.	85% 5-bromoacenaphthene	(11)
Phenanthrene..........	NBS, CCl_4, 5 hr.	46% 9-bromophenanthrene	(11)
Anthracene..........	NBS, CCl_4, few minutes	58% 9-bromoanthracene	(11)
Benz[*a*]anthracene......	NBS, CCl_4	Good yield of 7-bromo derivative	(105)

TABLE 5—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Chrysene....	NBS, CCl_4	6-Bromochrysene	(105)
Pyrene.....	NBS, CCl_4	Excellent yield of 1-bromopyrene	(105)
Phenol..	NBA, ether, 12 hr., cold	*p*-Bromophenol	(99)
Anisole.....	1/3NBS, 16 hr.	32% *p*-bromoanisole	(11)
	NBA, acetone, 24 hr., room temperature	75% *p*-bromoanisole	(99)
Phenetole............ .	1/2NBS, 16 hr.	20% *p*-bromophenetole	(11)
3-Methoxytoluene......	1/2NBS	49% 6-bromo-3-methoxytoluene	(11)
1,4-Dimethoxybenzene.	1/2NBS, CCl_4, 12 hr.	73% 2-bromo-1,4-dimethoxybenzene	(11)
1,2-Dimethoxybenzene	1/2NBS, CCl_4, 6 hr.	62% 4-bromo-1,2-dimethoxybenzene	(11)
1,3-Dimethoxybenzene.	1/2NBS, CCl_4, 6 hr.	82% 4-bromo-1,3-dimethoxybenzene	(11)
1-Methoxynaphthalene.	2/3NBS, CCl_4	79% 4-bromo-1-methoxynaphthalene	(11)
2-Methoxynaphthalene.	2/3NBS, CCl_4, 15 min.	94% 1-bromo-2-methoxynaphthalene	(11)
2-Ethoxynaphthalene...	NBS, CCl_4, 15 min.	79–88% 1-bromo-2-ethoxynaphthalene	(11)
2-Methoxy-6-methylnaphthalene.....	NBS, CCl_4, 4–5 hr.	71% 1-bromo-2-methoxy-6-methylnaphthalene	(74, 75)
Methyl phenyl sulfide..	NBS, CCl_4	Poor yield of methyl *p*-bromophenyl sulfide	(11)
Phenyl acetate.........	1/2NBS, vigorous reaction	37% *p*-bromophenyl acetate, considerable amount of *o*-bromo isomer	(11)
Acetanilide............	NBS, CCl_4, 1 hr.	Quantitative yield of *p*-bromoacetanilide	(11)
Dimethylaniline.......	1/3NBS, CCl_4, 15 min.	71% *p*-bromodimethylaniline	(11)
Estradiol............	2NBA, ethanol, 18 hr., room temperature	94% 2,4-dibromoestradiol	(101)
(*2*) *"Side chain" bromination:*			
Toluene . . .. ,	NBP	Benzyl bromide	(9)
	NBS, CCl_4, 45 min., peroxide	64% benzyl bromide	(86)
o-Chlorotoluene... .. .	1/2NBS, CCl_4, 2½ hr.	83% *o*-chlorobenzyl bromide	(4)
p-Nitrotoluene	*ca.* 1/2NBS, CCl_4, 12 hr.	50% *p*-nitrobenzyl bromide	(11)
Indene..	1/2NBS, CCl_4, 24 hr.	51% 1-bromoindene	(11)
Tetralin..............	2NBS, CCl_4, 1/2 hr., peroxide, then CH_3-COOK	74% naphthalene	(5, 122)
1,2-Dihydronaphthalene.....	NBS, CCl_4	Naphthalene and 15% 1,2-dibromotetralin	(122)

TABLE 5—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
1,4-Dihydronaphthalene	NBS, CCl_4	Naphthalene and 15% 2,3-dibromotetralin	(122)
1-Methylnaphthalene	NBS, CCl_4, 12 hr.	58% 1-naphthylmethyl bromide	(13)
2-Methylnaphthalene	1/2NBS, CCl_4, 6 hr.	80% 2-naphthylmethyl bromide	(11)
2-Methyl-3,4-dihydronaphthalene	NBS, then dehydrobrominate	2-Methylnaphthalene	(122)
1-Ethylnaphthalene	NBS, CCl_4, 12 hr., then dehydrobrominate	73% 1-vinylnaphthalene	(13)
1,2-Dimethylnaphthalene	NBS, CCl_4	Mixture of both monobromo compounds	(105)
1,6-Dimethylnaphthalene	NBS, CCl_4	Mixture	(105)
2,3-Dimethylnaphthalene	NBS	2-Bromomethyl-3-methylnaphthalene	(119)
2,6-Dimethylnaphthalene	NBS, CCl_4, 12 hr.	52% 6-bromomethyl-2-methylnaphthalene	(13)
2,7-Dimethylnaphthalene	NBS, CCl_4, 12 hr.	41% 7-bromomethyl-2-methylnaphthalene	(13)
1-Chloro-3,4-dihydronaphthalene	NBS, then dehydrobrominate	1-Chloronaphthalene	(122)
Acenapthene	NBS, CCl_4, peroxide, then CH_3COOK	20% acenapthylene	(5)
Diphenylmethane	NBS, (NBA), CCl_4, 1 hr.	81% diphenylmethyl bromide	(11)
Bibenzyl	NBS, CCl_4, peroxide, then CH_3COOK	56% stilbene, 10% stilbene dibromide	(5, 122)
p-Methylstilbene	NBS, CCl_4, 3 hr., peroxide	49% *p*-bromomethylstilbene	(118)
Triphenylmethane	NBS, CCl_4, vigorous reaction	55–62% triphenylmethyl bromide	(11)
Fluorene	NBS, CCl_4, 3 hr.	61% 9-bromofluorene	(98, 105, 112)
2-Nitrofluorene	NBS, CCl_4	9-Bromo-2-nitrofluorene	(105)
9-Phenylfluorene	NBS, CCl_4	9-Bromo-9-phenylfluorene	(11)
1,2,3,4-Tetrahydrophenanthrene	2 NBS, CCl_4, peroxide, then CH_3COOK	79% phenanthrene	(5)
as-Octahydrophenanthrene	4NBS, CCl_4, peroxide, then CH_3COOK	21% phenanthrene, 12% 1-bromophenanthrene (with 5.5NBS)	(5)

TABLE 5—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
sym-Octahydrophenanthrene	NBS, CCl_4, peroxide, then CH_3COOK	63% phenanthrene	(5)
sym-Octahydroanthracene	NBS, CCl_4, peroxide, then CH_3COOK	69% anthracene	(5)
Retene	NBS, CCl_4	1-Bromomethyl-7-isopropylphenanthrene	(105)

* NBS = *N*-bromosuccinimide.
NBA = *N*-bromoacetamide.
NBP = *N*-bromophthalimide.

TABLE 6

Wohl-Ziegler reaction with heterocyclic compounds

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
(*1*) *Oxygen heterocyclics:*			
2-Methylfuran	NBS,* CCl_4, 1/2 hr., cold	2-Bromomethylfuran (excellent yield)	(15)
2,5-Dimethylfuran	NBS, CCl_4, cold	2-Bromomethyl-5-methylfuran	(15)
Aucubin hexaacetate (2,3-disubstituted furan)	NBS, CCl_4, 1 hr., peroxide	Poor yield of monobromo derivative (substitution in 4- or 5-position)	(40)
Tetrahydro-γ-pyrone	NBS, CCl_4, 25 min., light	50% 3,5-dibromo derivative	(124)
2,6-Dimethyl-γ-pyrone	NBS, CCl_4, 1/2 hr.	2-Bromomethyl-6-methyl-γ-pyrone	(15)
3-Methylbenzofuran	NBS, CCl_4 (peroxide)	2-Bromo-3-methylbenzofuran	(23, 113)
	2NBS, CCl_4, 2 hr., peroxide	64% 2-bromo-3-bromomethylbenzofuran	(23)
2-Bromo-3-methylbenzofuran	NBS, CCl_4, peroxide	2-Bromo-3-bromomethylbenzofuran	(113)
2-Carbethoxy-3-methylbenzofuran	NBS, 130°C., 5 min.	65% 2-carbethoxy-3-bromobenzofuran	(113)
3-Methylcoumarin	NBS, CCl_4	3-Bromomethylcoumarin	(60)
4-Methylcoumarin	NBS, CCl_4	No reaction	(47)
6-Methylcoumarin	NBS, CCl_4	6-Bromomethylcoumarin (good yield)	(47)
4,6-Dimethylcoumarin	NBS, CCl_4	6-Bromomethyl-4-methylcoumarin	(47)
4,7-Dimethylcoumarin	NBS, CCl_4	7-Bromomethyl-4-methylcoumarin	(47)

TABLE 6—*Continued*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
7-Methoxy-4-methylcoumarin	NBS, CCl_4	3-Bromo-7-methoxy-4-methylcoumarin	(60)
3-Ethyl-7-methoxy-4-methylcoumarin	NBS, CCl_4	60% 3-(α-bromoethyl)-7-methoxy-4-methylcoumarin, 15% 6-bromo-3-ethyl-7-methoxy-4-methylcoumarin	(60, 120a)
3-Propyl-7-methoxy-4-methylcoumarin	NBS, CCl_4	3-(α-Bromopropyl)-7-methoxy-4-methylcoumarin	(120a)
(2) Nitrogen heterocyclics:			
α-Picoline	NBS	Easy bromination in side chain	(11)
γ-Picoline	NBS		(11)
Quinaldine	NBS		(11)
N-Benzoylindole	NBS	3-Bromo-*N*-benzoylindole	(11)
Carbazole	NBS, CCl_4, 7 min., peroxide	55% 3-bromocarbazole	(86)
Acridine	NBS, CCl_4, 5 hr., peroxide (8 hr. without peroxide)	Mono- and di-bromoacridines, *N*-(9-acridyl)-succinimide, several brominated derivatives of *N*-(9-acridyl)-succinimide, acridine hydrobromide, etc.	(87a)
1,3-Diacetyl-4-methyl-2-imidazolone	NBS, CCl_4, 20 min.	70% 1,3-diacetyl-4-bromomethyl-2-imidazolone	(109)
1,3-Diacetyl-4,5-dimethyl-2-imidazolone	NBS, CCl_4, 15 min.	82% 1,3-diacetyl-4-bromomethyl-5-methyl-2-imidazolone	(109)
	2NBS, CCl_4	50% 1,3-diacetyl-4,5-bis(bromomethyl)-2-imidazolone	
1,3-Diacetyl-4-methyl-5-(δ-carbomethoxyvaleryl)-2-imidazolone		See table 3	(108, 109)
(3) Sulfur heterocyclics:			
Thiophene	NBA, 45 min.	52% 2-bromothiophene	(89)
	2.5NBA, 45 min., then 5 hr., room temperature	65% 2,5-dibromothiophene	(89)
	1/6NBS, 24 hr.	77% 2-bromothiophene	(11)

TABLE 6—*Concluded*

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
2-Methylthiophene	NBS, CCl_4, 5 hr.	66% 2-methyl-5-bromothiophene, 24% 2-bromomethylthiophene	(107)
	NBS, CCl_4, 5 hr., peroxide	84% 2-bromomethylthiophene, 16% 2-methyl-5-bromothiophene	
	2NBS, CCl_4, 5 hr., with or without peroxide	2-Bromomethyl-5-bromothiophene	
3-Methylthiophene. . .	NBS, CCl_4, 5 hr.	90% 2-Bromo-3-methylthiophene	(106. 107)
	NBS, CCl_4, 6 hr., peroxide	65–90% 3-bromomethylthiophene, small amount of 2-bromo-3-methylthiophene	(106, 107)
	2NBS, CCl_4, 5 hr.	Chiefly 2, 5-dibromo-3-methylthiophene	(107)
	2NBS, CCl_4, 5 hr., peroxide	Chiefly 2-bromo-3-bromomethylthiophene	(107)
2,5-Dimethylthiophene.	NBS, CCl_4, few minutes, 60°C.	37% 2-bromomethyl-5-methylthiophene	(15)
3-Bromo-2,5-dimethylthiophene............	NBS	3-Bromo-2-bromomethyl-5-methylthiophene and 3-bromo-5-bromomethyl-2-methylthiophene	(119)
Thianaphthene.........	NBS, CCl_4, 36 hr.	3-Bromothianaphthene	(15)

* NBS = *N*-bromosuccinimide.
NBA = *N*-bromoacetamide.

TABLE 7

Wohl–Ziegler reaction with miscellaneous compounds

COMPOUND	REACTION CONDITIONS	YIELD OF PRODUCT	REFERENCES
Malonic ester half-amide..	NBA,* acetone, 24 hr., cold	Monobromo derivative	(99)
tert-Butyl bromide.....	NBA, ether, cold	15% isobutylene bromide	(99)
1-Phenyl-1-propyne	NBA, ether, 24 days, room temperature	45% dibromo derivative	(100)
Decalin................	NBS, CCl_4, 20 min., peroxide	*x*-Tetrabromoöctalin	(5)
	4NBS	14% *x*-tetrabromoöctalin, 9% 1,5-dibromonaphthalene	

* NBA = *N*-bromoacetamide.
NBS = *N*-bromosuccinimide.

(17) Cope, A. C., and Bailey, W. J.: J. Am. Chem. Soc. **70**, 2305 (1948).
(18) Dauben, H. J., and Wenkert, E.: J. Am. Chem. Soc. **69**, 2074 (1947).
(19) Djerassi, C., and Scholz, C. R.: Experientia **3**, 107 (1947).
(20) Djerassi, C., and Scholz, C. R.: J. Am. Chem. Soc. **69**, 2404 (1947).
(21) Djerassi, C.: Unpublished observation.
(22) English, J., and Gregory, J. D.: J. Am. Chem. Soc. **69**, 2123 (1947).
(23) Erlenmeyer, H., and Grubenmann, W.: Helv. Chim. Acta **30**, 297 (1947).
(24) Ettlinger, M. G., and Fieser, L. F.: J. Biol. Chem. **164**, 451 (1946).
(25) Ettlinger, M. G.: Ph.D. Dissertation, Harvard University, 1945.
(26) Fieser, L. F., and Campbell, W. P.: J. Am. Chem. Soc. **60**, 159, 2631 (1938); **61**, 2528 (1939).
(27) Flaig, W.: Report No. 52025, Office of the Publication Board, U. S. Department of Commerce; Chem. Abstracts **41**, 6189 (1947).
(28) Fuson, R. C., Arnold, R. T., and Cooke, H. G.: J. Am. Chem. Soc. **60**, 2272 (1938).
(29) Fuson, R. C., and Southwick, P. L.: J. Am. Chem. Soc. **66**, 679 (1944).
(30) Glattfeld, J. W. E., and Rietz, E.: J. Am. Chem. Soc. **62**, 974 (1940).
(31) Groll, H. P. A., and Hearne, G.: Ind. Eng. Chem. **31**, 1530 (1939). For earlier references see Burgin, J., Engs, W., Groll, H. P. A., and Hearne, G.: Ind. Eng. Chem. **31**, 1413 (1939).
(32) Henbest, H. B., Jones, E. R. H., Bide, A. E., Peevers, R. W., and Wilkinson, P. A.: Nature **158**, 169 (1946).
(33) Heilbron, I., Jones, E. R. H., and O'Sullivan, D. G.: Nature **157**, 485 (1946); J. Chem. Soc. **1946**, 866.
(34) Hey, D. H.: Nature **156**, 36 (1945).
(35) Hey, D. H.: Ann. Repts. Progress Chem. (Chem. Soc. London) **41**, 181 (1944).
(36) Howton, D. R.: J. Am. Chem. Soc. **69**, 2060 (1947).
(37) Howton, D. R., and Buchman, E. R.: J. Am. Chem. Soc. **70**, 2517 (1948) and later paper.
(38) Jeger, J., Duerst, O., and Buechi, G.: Helv. Chim. Acta **30**, 1853 (1947).
(39) Karrer, P., and Rutschmann, J.: Helv. Chim. Acta **28**, 793 (1945).
(40) Karrer, P., and Schmid, H.: Helv. Chim. Acta **29**, 525 (1946).
(41) Karrer, P., Jucker, E., and Schick, E.: Helv. Chim. Acta **29**, 704 (1946).
(42) Karrer, P., and Schwyzer, R.: Helv. Chim. Acta **29**, 1191 (1946).
(43) Karrer, P., and Ringli, W.: Helv. Chim. Acta **30**, 863 (1947).
(44) Karrer, P., and Ringli, W.: Helv. Chim. Acta **30**, 1771 (1947).
(45) Karrer, P., and Alagil, H.: Helv. Chim . Acta **30**, 1776 (1947).
(45a) Karrer, P., and Ochsner, P.: Helv. Chim. Acta **30**, 2092 (1947).
(46) Kharasch, M. S., and Priestley, H. M.: J. Am. Chem. Soc. **61**, 3425 (1939).
(47) Lecocq, J., and Buu-Hoï: Compt. rend. **224**, 937 (1947).
(48) Massie, S. M.: Ph.D. Dissertation, Iowa State College, 1946, p. 105; see Iowa State Coll. J. Sci. **21**, 41 (1946).
(49) Meystre, C., Frey, H., Wettstein, A., and Miescher, K.: Helv. Chim. Acta **27**, 1815 (1944).
(50) Meystre, C., Ehmann, L., Neher, R., and Miescher, K.: Helv. Chim. Acta **28**, 1252 (1945).
(51) Meystre, C., and Miescher, K.: Helv. Chim. Acta **28**, 1497 (1945).
(52) Meystre, C., and Miescher, K.: Helv. Chim. Acta **29**, 33 (1946).
(53) Meystre, C., Frey, H., Neher, R., Wettstein, A., and Miescher, K.: Helv. Chim. Acta **29**, 627 (1946).
(54) Meystre, C., and Wettstein, A.: Experientia **2**, 408 (1946).
(55) Meystre, C., and Wettstein, A.: Experientia **3**, 185 (1947).
(56) Meystre, C., Wettstein, A., and Miescher, K.: Helv. Chim. Acta **30**, 1022 (1947).
(57) Meystre, C., and Wettstein, A.: Helv. Chim. Acta **30**, 1037 (1947).
(58) Meystre, C., and Wettstein, A.: Helv. Chim. Acta **30**, 1256 (1947).

(58a) Miescher, K.: Helv. Chim. Acta **29**, 743 (1946).

(59) Moffett, R. B., Stafford, J. E., Linsk, J., and Hoehn, W. M.: J. Am. Chem. Soc. **68**, 1857 (1946).

(60) Molho, D., and Mentzer, C.: Compt. rend. **223**, 1141 (1946).

(61) Mousseron, M., Winternitz, F., and Jacquier, R.: Compt. rend. **224**, 1062 (1947).

(62) Newbold, G. T., and Spring, F. S.: J. Chem. Soc. **1944**, 532.

(63) Plattner, P. A., and Klaeui, H.: Helv. Chim. Acta **26**, 1553 (1943).

(64) Plattner, P. A., and Heusser, H.: Helv. Chim. Acta **29**, 727 (1946).

(65) Plattner, P. A., Ruzicka, L., Heusser, H., Pataki, J., and Meier, K.: Helv. Chim. Acta **29**, 942 (1946).

(66) Plattner, P. A., Ruzicka, L., Heusser, H., and Angliker, E.: Helv. Chim. Acta **30**, 385 (1947).

(67) Plattner, P. A., Ruzicka, L., Heusser, H., and Angliker, E.: Helv. Chim. Acta **30**, 395 (1947).

(68) Plattner, P. A., Meier, K., and Heusser, H.: Helv. Chim. Acta **30**, 905 (1947).

(69) Putokhin, N. I.: J. Gen. Chem. (U.S.S.R.) **15**, 332 (1945); Chem. Abstracts **40**, 3741 (1946).

(70) Rabe, P.: Ber. **44**, 2088 (1911).

(71) Rabe, P., and Kindler, K.: Ber. **51**, 466 (1918).

(72) Raphael, R. A.: Nature **160**, 261 (1947).

(73) Robertson, A., and Waters, W. A.: J. Chem. Soc. **1947**, 492.

(74) Royer, R., and Buu-Hoï: Compt. rend. **222**, 746 (1946).

(75) Royer, R.: Ann. chim. [12] **1**, 395 (1946).

(76) Ruggli, P., and Schmidlin, J.: Helv. Chim. Acta **29**, 383 (1946).

(77) Ruggli, P., and Schmidlin, J.: Helv. Chim. Acta **29**, 396 (1946).

(78) Rust, F. F., and Vaughan, W. E.: J. Org. Chem. **5**, 472 (1940).

(79) Ruzicka, L., Jeger, O., and Redel, J.: Helv. Chim. Acta **26**, 1235 (1943).

(80) Ruzicka, L., Jeger, O., and Ingold, W.: Helv. Chim. Acta **27**, 1859 (1944).

(81) Ruzicka, L., Plattner, P. A., and Pataki, J.: Helv. Chim. Acta **28**, 1360 (1945).

(82) Ruzicka, L., Plattner, P. A., and Heusser, H.: Helv. Chim. Acta **29**, 473 (1946).

(83) Ruzicka, L., Plattner, P. A., Heusser, H., and Pataki, J.: Helv. Chim. Acta **29**, 936 (1946).

(84) Ruzicka, L., Plattner, P. A., Heusser, H., and Meier, K.: Helv. Chim. Acta **30**, 1342 (1947).

(85) Salamon, I., and Reichstein, T.: Helv. Chim. Acta **30**, 1616 (1947).

(86) Schmid, H., and Karrer, P.: Helv. Chim. Acta **29**, 573 (1946).

(87) Schmid, H.: Helv. Chim. Acta **29**, 1144 (1946).

(87a) Schmid, H., and Leutenegger, W. E.: Helv. Chim. Acta **30**, 1965 (1947).

(88) Soloway, S. B., and Laforge, F. B.: J. Am. Chem. Soc. **69**, 979 (1947).

(89) Steinkopf, W., and Otto, A.: Ann. **424**, 61 (1921).

(90) Stork, G.: Private communication.

(91) Vaughan, W. E., Rust, F. F., and Hearne, G. W.: Nature **156**, 53 (1945).

(92) Waters, W. A.: J. Chem. Soc. **1937**, 2007.

(93) Waters, W. A.: Nature **154**, 772 (1944); see also *The Chemistry of Free Radicals*, pp. 252–6, University Press, Oxford (1946).

(94) Waters, W. A.: Nature **156**, 53 (1945).

(95) Wendt, G.: Ber. **74**, 1242 (1941).

(96) Wettstein, A., and Meystre, C.: Helv. Chim. Acta **30**, 1262 (1947).

(97) Wieland, P., and Miescher, K.: Helv. Chim. Acta **30**, 1876 (1947).

(98) Wittig, G., and Felletschin, G.: Ann. **555**, 133 (1944).

(99) Wohl, A.: Ber. **52**, 51 (1919).

(100) Wohl, A., and Jaschinowski, K.: Ber. **54**, 476 (1921).

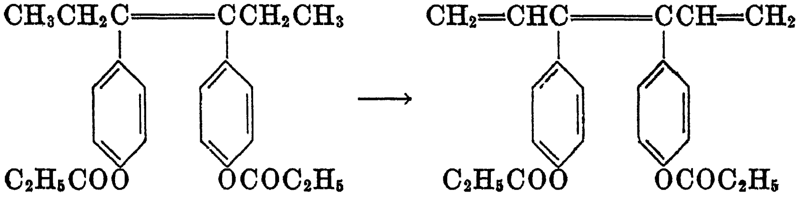
(101) Woodward, R. B.: J. Am. Chem. Soc. **62**, 1625 (1940).

(102) Ziegler, K., Schenck, G., Krockow, E. W., Siebert, A., Wenz, A., and Weber, H.: Ann. **551**, 1 (1942).
(103) Ziegler, K., Spaeth, A., Schaaf, E., Schumann, W., and Winkelmann, E.: Ann. **551**, 80 (1942).
(104) Ziegler, K., Schumann, W., and Winkelmann, E.: Ann. **551**, 120 (1942).

VIII. Appendix

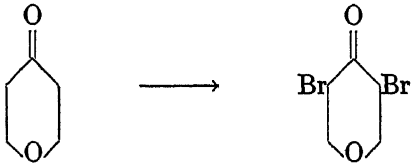
The appendix covers the literature up to June 1, 1948 and the additional material has also been incorporated into the tables.

Freiman (111) showed that diethylstilbestrol dipropionate (LXXX) reacted with 2 moles of *N*-bromosuccinimide to yield a dibromo compound which could be dehydrobrominated to the corresponding hexatriene derivative (LXXXI).



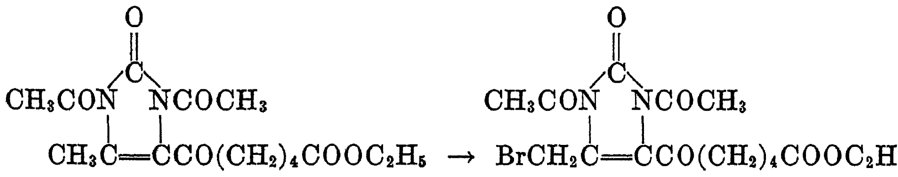
LXXX LXXXI

The bromination of tetrahydro-γ-pyrone (LXXXII) represents another example of the bromination of a saturated ketone with *N*-bromosuccinimide and is reported to lead to the 3,5-dibromoketone LXXXIII (125), which could be converted to γ-pyrone on treatment with pyridine. Free bromine gave only traces of the desired product.

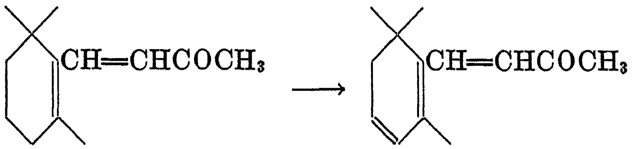


LXXXII LXXXIII

Further confirmation of the statement that bromination of α,β-unsaturated ketones occurs in the allyl position, unless blocked, is afforded by reports on the reaction of *N*-bromosuccinimide with the imidazolone LXXXIV which gave LXXXV (108, 109) and β-ionone (LXXXVI) (115), which after dehydrobromination yielded dehydro-β-ionone (LXXXVII). The latter represents a promising starting material for the synthesis of dehydrovitamin A_1 (114, 115), which is of considerable interest since it may be identical with vitamin A_2.

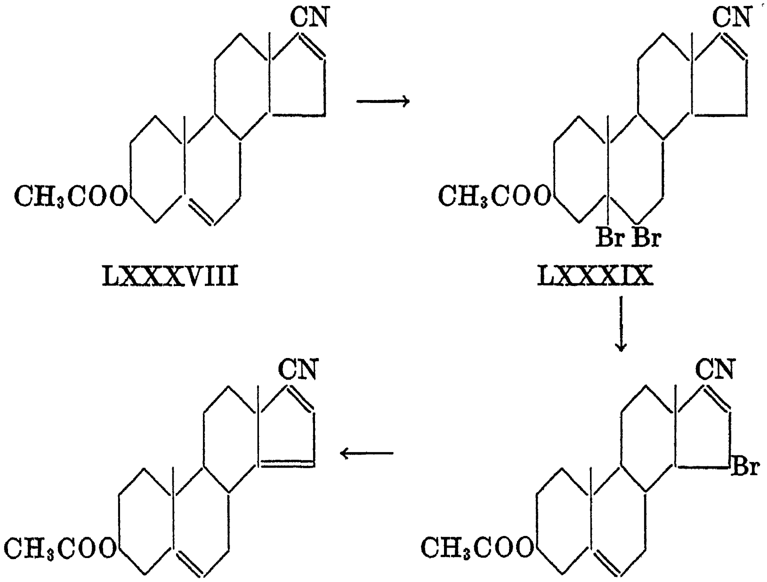

O
C
CH_3CON
$NCOCH_3$
CH_3C=$CCO(CH_2)_4COOC_2H_5$
O
C
CH_3CON
$NCOCH_3$
$BrCH_2C$=$CCO(CH_2)_4COOC_2H_5$

LXXXIV LXXXV



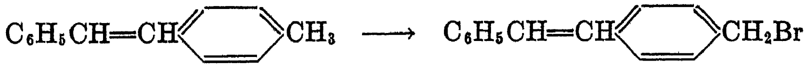
LXXXVI LXXXVII

Plattner and coworkers (123) described an apparently general method for the introduction of the 14,15-double bond into steroids which contain also unsaturation in ring B. The procedure was illustrated with the choladienenitrile LXXXVIII, in which the 5,6-double bond was protected with bromine and LXXXIX was treated with *N*-bromosuccinimide to afford after debromination the 15-bromo derivative (XC). Dehydrobromination of the latter in the usual manner gave an 80 per cent over-all yield (based on LXXXVIII) of the desired triene XCI.



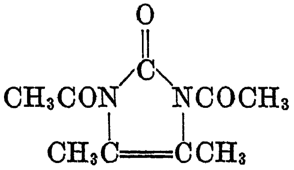
LXXXVIII LXXXIX XC XCI

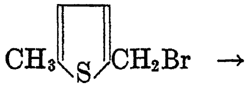
In continuation of earlier work, Buu-Hoï and Lecocq (105) showed that higher polycyclic hydrocarbons such as pyrene and chrysene were readily monobrominated with *N*-bromosuccinimide. Mousseron and coworkers (122) investigated the action of *N*-bromosuccinimide on hydroaromatic compounds and obtained essentially the same results as Barnes (5). Their report, however, that fluorene does not react with *N*-bromosuccinimide is incorrect (98, 105, 112). As a route to 4-styrylbenzylamines, Kon (118) investigated the action of *N*-bromosuccinimide on *p*-methylstilbene (XCII) and observed side-chain bromination (XCIII) in the presence of peroxide.

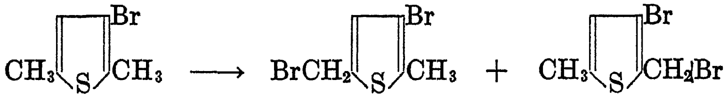


XCII XCIII

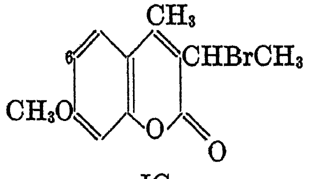
Interesting experiments have been reported with heterocyclics. Imidazolones such as XCIV could readily be mono- or di-brominated in the methyl groups (109). Lecocq and Buu-Hoï (119) observed that 2-bromomethyl-5-methylthiophene (XCV) on treatment with cyanide underwent a rearrangement to the 3-bromo-2,5-dimethylthiophene (XCVI). Carbonation of the Grignard reagent of XCV led to similar results, and so did the higher substituted thiophene derivative XCVII. The latter as well as XCVIII (which did not rearrange, the 3-position being blocked in this instance) were obtained from XCVI and *N*-bromosuccinimide.


XCIV


XCV


XCVI XCVII XCVIII

Similarly, 3-methylthiophene reacted with *N*-bromosuccinimide in the methyl group (106, 107), especially when peroxide was used. The resulting 3-thenyl bromide also seemed to undergo a partial rearrangement to 2-bromo-3-methylthiophene (106). In the absence of peroxide, 2- and 3-methylthiophenes underwent predominantly nuclear bromination (107). An unusual rearrangement of a bromine atom from the 3-ethyl group of the coumarin derivative IC to the 6-position has been reported (120a). No explanation was advanced and the structure of the product was not demonstrated unequivocally.


IC

The reaction of 3-methylbenzofuran (LXXVII) with *N*-bromosuccinimide has been investigated further by Grubenmann and Erlenmeyer (113), who showed that bromination in the methyl group was achieved readily when the 2-position was blocked.

References to appendix

(105) Buu-Hoï and Lecocq, J.: Compt. rend. **226**, 87 (1948).
(106) Campaigne, E., and Lesuer, W. M.: J. Am. Chem. Soc. **70**, 1555 (1948).
(107) Dittmer, K., Martin, R. P., Herz, W., and Cristol, S.: J. Am. Chem. Soc., in press.
(108) Duschinsky, R., and Dolan, L. A.: Jubilee Volume Emil Barell **1946**, 164.

(109) DUSCHINSKY, R., AND DOLAN, L. A.: J. Am. Chem. Soc. **70**, 657 (1948).
(110) FARMER, E. H., AND SHIPLEY, F. W.: J. Chem. Soc. **1947**, 1519.
(111) FREIMAN, M. J.: J. Am. Chem. Soc. **70**, 1278 (1948).
(112) FUSON, R. C., AND PORTER, H. D.: J. Am. Chem. Soc. **70**, 895 (1948).
(113) GRUBENMANN, W., AND ERLENMEYER, H.: Helv. Chim. Acta **31**, 78 (1948).
(114) HEILBRON, I.: J. Chem. Soc. **1948**, 386.
(115) HENBEST, H. B.: Nature **161**, 481 (1948).
(116) HENBEST, H. B., AND JONES, E. R. H.: J. Chem. Soc., in press.
(117) KARRER, P., AND SCHNEIDER, P.: Helv. Chim. Acta **31**, 395 (1948).
(118) KON, G. A. R.: J. Chem. Soc. **1948**, 224.
(119) LECOCQ, J., AND BUU-HOÏ: Compt. rend. **224**, 658 (1947).
(120) MILLER, F. A., AND KOCH, S. D.: J. Am. Chem. Soc. **70**, 1890 (1948).
(120a) MOLHO, D., AND MENTZER, C.: Compt. rend. **224**, 471 (1947).
(121) MOSER, C., AND STORK, G.: Private communication.
(122) MOUSSERON, M., MANON, AND WINTERNITZ, F.: Bull. soc. chim. France **1947**, 759.
(123) PLATTNER, P. A., HEUSSER, H., AND SEGRE, A.: Helv. Chim. Acta **31**, 249 (1948).
(124) ROBERTS, J. D., AND TRUMBULL, E. R.: Abstracts of Papers Presented at the 114th Meeting of the American Chemical Society, St. Louis, Missouri, September, 1948, p. 43L.
(125) SORKIN, E., KRAEHENBUEHL, W., AND ERLENMEYER, H.: Helv. Chim. Acta **31**, 65 (1948).

THE SCATTERING OF LIGHT AND ITS APPLICATIONS TO CHEMISTRY

GERALD OSTER

Rockefeller Institute for Medical Research, Princeton, New Jersey

Received January 19, 1948

CONTENTS

I. Introduction . . . 319
II. Independent particles . . . 320
  A. Small particles . . . 320
    1. Isotropic particles . . . 320
    2. Anisotropic particles . . . 326
  B. Large particles . . . 328
    1. Large spheres . . . 328
    2. Metallic particles . . . 334
    3. Large particles with relative index of refraction near unity . . . 335
    4. Depolarization by large particles . . . 344
III. Non-independent particles . . . 349
    1. Pure liquids . . . 350
    2. Non-ideal solutions . . . 354
    3. Liquids at the critical temperature . . . 356
    4. Interfaces . . . 357
    5. Fine structure of the Rayleigh line . . . 358
IV. References . . . 360

I. INTRODUCTION

When a beam of light falls upon matter, the electric field associated with the light induces periodic oscillations of the electrons in the material. The material then serves as a secondary source of light and radiates light in the form of scattered radiation with a wave length equal to that of the incident light.[1] The intensity, polarization, angular distribution, and fine structure of the scattered radiation are determined by the size, shape, optical constants, and interactions of the molecules in the scattering material. Conversely, from a knowledge of the light-scattering properties of a given system, the chemist can, with the aid of the electromagnetic theory of radiation and the kinetic theory of matter, obtain a detailed molecular picture of that system.

The use of light scattering to study molecular systems has the added advantage that the system under study is not affected by the measurement (except in the rare instances in which the incident light induces photochemical changes) and that changes in the system which take place rapidly can be easily followed.

In this review no attempt will be made to discuss all the problems to which light scattering has been (or could be) applied, since such a discussion would encompass nearly every branch of science. We shall, instead, confine ourselves to the physical principles of light scattering and to the chemical problems to which it has been applied and shall indicate some further possible uses for it in the field of chemistry.

---

[1] In this paper we shall not consider the relatively small amount of light which is re-emitted with an altered wave length when the molecules are raised to higher energy states by the incident light, i.e., the Raman effect (compare Section III,5).

II. INDEPENDENT PARTICLES

Independent particles are defined as particles located randomly in space, as are molecules in a perfect gas or solute molecules in an ideal solution. For a system of independent particles, the intensity of the light scattered is the sum of the contributions from each of the scattering particles of the system. Since the particles are randomly disposed, the light scattered by any one particle bears no fixed relationship to that for any other particle, i.e., there is incoherent scattering, and the total intensity of scattered light is the sum of the intensities from all the particles. If, however, the scattering elements lie close together in a regular array, as in a perfect crystal at zero absolute temperature, there is destructive interference between the scattered wavelets because of the fixed phase relationships, i.e., there is coherent scattering, and the intensity of scattered light is zero. Because of the imperfect correlation which exists between the positions of molecules in a liquid, a liquid will scatter light with intensity intermediate between that for the same weight of a gas and that for a crystal.

In the case of particles which possess a linear dimension comparable to or greater than the wave length of incident light, the scattering from different parts of the same particle must be considered. Because there are fixed phase relationships between the wavelets scattered from the scattering elements of the same particle, there is for large particles some destructive interference with a consequent decrease in efficiency of scattering. Nevertheless, the intensity of light scattered by a system of large particles randomly disposed will be the sum of the contributions of the light scattered from each of the particles.

A. SMALL PARTICLES

1. Isotropic particles

Lord Rayleigh in 1871 (172) laid the foundation of light scattering by his application of electromagnetic theory to the problem of light scattering by molecules in a gas. He subsequently (173) used his results to account for the observed intensity, color, and polarization of light from the sky. According to Rayleigh (172, 173) the oscillating electric field of the light incident upon a transparent optically isotropic particle whose radius is small compared with the wave length of the light induces an oscillating electric moment in the particle. The particle, acting as a linear electrical oscillator, does not radiate light in the direction of the vibrations. Along other directions, however, it radiates light and the scattered light is perfectly plane polarized when viewed at right angles to the incident beam whether the incident light is polarized or unpolarized. The first detailed observations on the polarization of scattered light were made by Tyndall (208).

The character of the scattered light from particles small compared with the wave length of the incident light is given by the formula for the intensity of radiation from a Hertzian dipole antenna which is derived in most textbooks of theoretical physics (see, for example, Slater and Frank (190, Chapter 25)). It is shown that the intensity of scattered light is proportional to the inverse fourth power of the wave length. Thus, when white light is made to fall on a system of such particles, the blue component of the white light is scattered much more than is the red; and the system has a blue color when viewed at right angles to the incident beam of light. When viewed in the direction of the transmitted beam, the system appears yellow in color since the blue component has been removed by scattering.

The complete equation for the intensity of light scattered by ν (per unit volume) independent small isotropic scatterers is derived in detail in treatises on electromagnetic theory (Born (19, Chapter 7, Section 81); Stratton (199, Chapter 8, Section 8.5 and Chapter 9, Section 9.27)) and is given by

$$\frac{i}{I} = \frac{8\pi^4 \nu \alpha^2}{\lambda'^4 r^2}(1 + \cos^2 \theta) \tag{1}$$

i is the intensity of scattered light per unit volume of the scattering system, I is the intensity of the incident beam, r is the distance of the observer from the scattering system, θ is the angle between the observer and the proceeding incident beam, λ' is the wave length of the light falling on the particles ($\lambda' = \lambda/n_0$, where λ is the wave length of light incident upon the system and n_0 is the index of refraction of the medium), and α is the polarizability or induced dipole moment per unit electrical field strength of the small isotropic particles. Equation 1 is for unpolarized incident light; the $\cos^2 \theta$ term in the parentheses refers to the component of the scattered light whose electric vector lies in the plane defined by the incident and scattered beams (the plane of the page in figure 1) and the unity term in the parentheses refers to the component of the scattered light whose electric vector is perpendicular to this plane. Figure 1 shows the angular distribution of intensity and polarization of the light scattered from a small isotropic scatterer. The scatterer is at the origin, and the length of the line drawn from the origin to a point on the curve is proportional to the intensity of scattered light. The dotted curve refers to the $\cos^2 \theta$ term, that is, to the component which is horizontally polarized, and the outer curve refers to the component which is vertically polarized. It is seen from figure 1 that the light scattered at 90° is completely vertically plane polarized. The total intensity of scattered light is the sum of the horizontally and vertically polarized components given by equation 1. The spacial distribution of the intensity of the scattered light is given by the surface formed by rotating the curves in figure 1 about the vertical axis.

When a beam of light traverses a light-scattering system, its intensity is decreased by virtue of the energy withdrawn from the beam in the form of scattered radiation. The energy lost is given by the time average of Poynting's vector integrated over the surface of a sphere of radius r. For small isotropic scatterers the angular intensity distribution is symmetrical; i.e., the intensity of scattered light in the forward directions is equal to that in the backward directions, and the fractional decrease in intensity of the incident light scattered in all directions can be calculated. The logarithm of the fractional decrease in transmitted intensity, I, is given by the turbidity τ (also called the attenuation or extinction coefficient due to scattering) where $I = I_0 e^{-\tau l}$ and l is the path length in the scattering system. Such a calculation (Born (19, page 377); Stratton (199, page 436)) shows that for i perpendicular to the incident beam ($\theta = 90°$)

$$\tau = \frac{16}{3}\pi r^2 \frac{i}{I} \tag{2}$$

and on combining with equation 1 we obtain for the turbidity:

$$\tau = \frac{128\pi^5 \nu \alpha^2}{3\lambda'^4} \tag{3}$$

Since by equation 3 the turbidity for independent particles is proportional to the number of particles per unit volume, ν, equation 3 is a statement of Beer's law where the attenuation in intensity of the incident light is due to scattering.

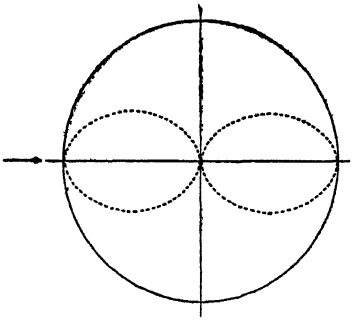


FIG. 1. Angular scattering diagram for small isotropic particle (dipole scattering). See text for explanation.

The polarizability of an isotropic molecule is proportional to the volume of the molecule; therefore from equations 1 and 3 the intensity of scattering is proportional to the number concentration, ν, of the particles and the square of their volumes. Because of the strong dependence of the intensity of scattering on the volume of the particles, it is important in scattering measurements to eliminate large extraneous particles (usually dust) which scatter a considerable amount of light even though they are present in relatively small concentrations. The practically complete elimination of dust particles in gases for light-scattering studies was first achieved by Cabannes in 1915 (23).

In order to relate equations 1 and 3 to experimental quantities, it is necessary to introduce the optical constants of the system. For a mixture of ν isotropic particles (per unit volume) of polarizability α immersed in a medium of optical dielectric constant ϵ_0 (the optical dielectric constant of transparent material is equal to the square of its refractive index) the following relation holds

$$\frac{\epsilon - \epsilon_0}{\epsilon_0} = 4\pi\nu\alpha \tag{4}$$

where ϵ is the optical dielectric constant of the mixture. Equation 4, which is due to Maxwell (see Jeans (90a, Chapter 5)), is valid regardless of the shape of the isotropic particles and requires no assumptions concerning the electric field on the particles (the local field). Inserting equation 4 into equations 1 and 3, we obtain for the intensity (per unit volume) and turbidity of the small isotropic particles (note that $\lambda = n_0\lambda'$)

$$\frac{i}{I_0} = \frac{\pi^2(\epsilon - \epsilon_0)^2}{2\lambda^4 \nu r^2}(1 + \cos^2\theta) \tag{5}$$

and

$$\tau = \frac{8\pi^3(\epsilon - \epsilon_0)^2}{3\lambda^4 \nu} \tag{6}$$

Cabannes (24) has made quantitative measurements on the intensity of light scattered by argon. He was able to determine the number of gas molecules per unit volume, ν, from equation 5 where $\epsilon_0 = 1$ (empty space). Since $\nu = Nc/M$, where N is Avogadro's number, c the weight concentration, and M the molecular weight, Cabannes obtained a value for Avogadro's number.

Inserting Nc/M for ν in equations 5 and 6 we obtain expressions relating the intensity of scattering (per unit volume) and the turbidity to the molecular weight of the scatterers, or

$$\frac{i}{I_0} = \frac{\pi^2 Mc}{2\lambda^4 r^2 N}\left(\frac{\epsilon - \epsilon_0}{c}\right)^2(1 + \cos^2\theta) \tag{7}$$

and

$$\tau = \frac{8\pi^3 Mc}{3\lambda^4 N}\left(\frac{\epsilon - \epsilon_0}{c}\right)^2 \tag{8}$$

The specific dielectric increment, $\epsilon - \epsilon_0/c$, may be expressed in terms of the specific index of refraction increment, $n - n_0/c$, where n and n_0 are the indices of refraction of the mixture and medium, respectively, by

$$\frac{\epsilon - \epsilon_0}{c} = \frac{n^2 - n_0^2}{c} \simeq \frac{\partial n^2}{\partial c} \simeq 2n_0\left(\frac{n - n_0}{c}\right) \tag{9}$$

For most substances the specific index of refraction increment is a constant independent of the concentration and depends on the index of refraction of the solute and of the medium. In the extreme case in which the index of refraction of the medium is equal to that of the solute, the refractive index increment is zero and no scattering will take place. The index of refraction of isotropic solute particles may be determined by adjusting the refractive index of the medium until no scattering occurs (Heller (84)).

Putzeys and Brosteaux (154, 155) have determined the relative intensity of scattering from dilute solutions of a few proteins. They found that the intensities were proportional to the known molecular weights of these proteins, in agreement with equation 7. By their studies, Putzeys and Brosteaux were the first to establish the light-scattering method as a useful means of determining the molecular weights of large molecules in solution. Putzeys and Brosteaux (155) also determined the pH stability range of some proteins by measuring the relative intensity of scattering as a function of pH. In principle, they could have determined the absolute molecular weights from equation 8. In order to use this equation, however, it is necessary to know the volume of the scattering sample and the distance, r, very accurately. On the other hand, the absolute value of the turbidity can, for a sufficiently turbid sample, conveniently be measured in a colorimeter or spectrophotometer and only the thickness of the sample need be known (see below).

From equation 8, using the approximation of equation 9, the molecular weight of the small isotropic colorless solute particles is related to the turbidity for very dilute solutions (the turbidity of the solvent is subtracted) by

$$M = \frac{\tau}{Hc} \tag{10}$$

where

$$H = \frac{32\pi^3 n_0^2}{3N\lambda^4}\left(\frac{n - n_0}{c}\right)^2$$

Equation 10 is essentially Rayleigh's equation (equation 3) and is the result obtained from the more general expression due to Einstein (48) (see Debye (32, 33, 34) and Section III,2 of this paper), by extrapolating to infinite dilution. According to equation 10, the molecular weight of small isotropic particles can be determined from a knowledge of (*1*) the turbidity of a dilute solution of the material, (*2*) the concentration of the solution, and (*3*) the specific index of refraction increment.

An application of equation 10 was the determination of the molecular weights of tomato bushy stunt virus and influenza virus by the use of a spectrophotometer (Oster (138)). It was necessary to determine the turbidity as a function of wave length so as to use the turbidity in that wave-length region where the inverse fourth power of the wave-length relationship of Rayleigh was obeyed. The particles were large enough to give intense scattering where Beer's law was obeyed, so that the solutions were ideal. In figure 2 are shown the results for very dilute solutions of tomato bushy stunt virus. The turbidity given in terms of the optical density, D ($\tau = 2.303D$), obeys Rayleigh's inverse fourth power law over the visible range, but at shorter wave lengths there is real light absorption due to the presence of ultraviolet-absorbing chemical groups. The molecular weight calculated from the slopes of the curves, together with the index of refraction increments, gave values for the virus particles in agreement with those determined by other methods. The turbidity of the pure solvent is automatically taken care of when the turbidity of the solvent is taken as the zero reading in a spectrophotometer. The light-scattering method gives the molecular weights of the dry protein, since the water of hydration of the protein has nearly the same index of refraction as the solvent water. Recently Bardwell and

Sivertz (9) have determined the size of latex particles by the spectrophotometric method and obtained results in agreement with other methods.

The equations given above and the cases to which they were applied are those of monodispersed systems. Frequently, for high-polymeric and colloidal solutions, one does not deal with monodispersed systems. For a polydispersed system of ν_j (per unit volume) small isotropic particles of volume v_j, equation 3 for the turbidity is given by

$$\tau = A \sum_j \nu_j v_j^2 \tag{11}$$

where A is a function of the wave length and the proportionality constant (a function of the index of refraction) between the polarizability and the volume of the particles (see equation 18). Equation 11 may be used to obtain an expression for the turbidity as a function of time for some kinetic processes. For a solution of high-polymeric molecules or colloidal particles in which polymerization or coagulation is taking place, the system at any instant is polydispersed. If we know the number of j-mers, ν_j, as a function of time we can calculate the change in light scattering with time for the polymerization or coagulation process (Oster (139)). Since the volume of the j-mers is j times the volume of the monomers, v_0, equation 11 becomes

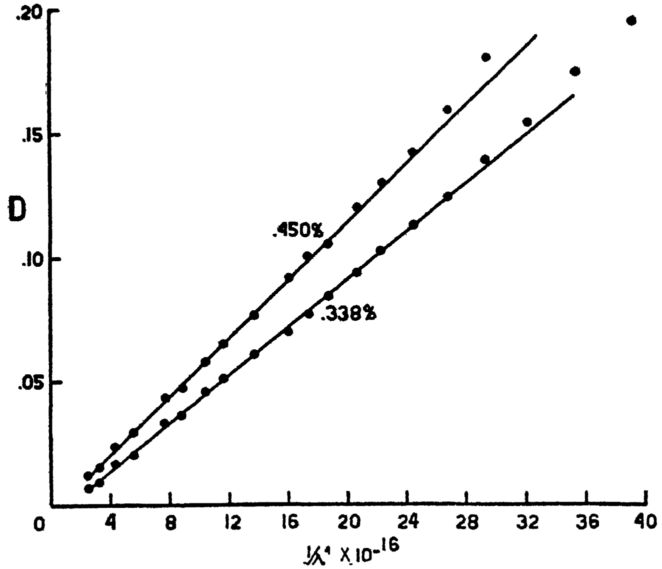


FIG. 2. Optical density as a function of inverse fourth power of the wave length for bushy stunt virus in water (Oster (138)).

$$\tau = A v_0^2 \sum_j j^2 \nu_j \tag{12}$$

The problem is now reduced to the mathematical one of evaluating the sum where ν_j is known for various polymerization and coagulation processes. Calculation shows (139) that (a) in linear condensation polymerization, the turbidity (or intensity of scattering) increases linearly with time with a slope determined by the rate constant of the elementary step reaction, (*b*) in depolymerization of linear polymers, the turbidity decreases with time as the hyperbolic cotangent of the time, (*c*) in addition polymerization, the turbidity increases quadratically in time with a curvature determined by the rate constant of the elementary step reaction, (*d*) in coagulation of colloidal particles, the turbidity increases linearly in time with a slope proportional to the square of the weight concentration of the colloid. The last case was confirmed from experiments on the turbidity of coagulating systems during the period in the process when the coagulating particles scattered light according to Rayleigh's law.

2. Anisotropic particles

In the previous discussion we considered optically isotropic particles, that is, particles whose polarizability, α, is independent of direction in the particle. For small isotropic particles, the direction of the electric field associated with the incident light always coincides with the direction of the induced moment, and the scattered light is perfectly plane polarized in the direction $\theta = 90°$. For anisotropic particles, however, in which the polarizabilities along the various directions in the particle are not equal, in that there are different refractive indices along different directions, the direction of the incident electric field may not coincide with the direction of the induced moment. As a consequence, the light scattered at 90° will not be perfectly plane polarized perpendicular to the plane of the incident beam and the direction of the observation, and will exhibit a weak component in the horizontal direction. Rayleigh (177) calculated the depolarization, i.e., the ratio of the intensity of the horizontally polarized light to that of the vertically polarized light, in terms of the polarizabilities, α_1, α_2, α_3, along the principal axes of the polarizability ellipsoid by resolving the induced dipole moments along these principal axes and integrating over all possible orientations of the particle. The expression for the depolarization, ρ_u, of the light scattered at 90° from unpolarized incident light is given by

$$\rho_u = \frac{2(\alpha_1^2 + \alpha_2^2 + \alpha_3^2 - \alpha_1\alpha_2 - \alpha_2\alpha_3 - \alpha_1\alpha_3)}{4(\alpha_1^2 + \alpha_2^2 + \alpha_3^2) + \alpha_1\alpha_2 + \alpha_2\alpha_3 + \alpha_1\alpha_3} \tag{13}$$

For such small anisotropic molecules, the intensity of light scattered will be more than that for particles which are of the same volume but which are isotropic. According to Cabannes (25), the intensity of scattered light given by equations 5 and 7 must be, for $\theta = 90°$, multiplied on the right-hand side by the factor

$$\frac{1 + \rho_u}{1 - \frac{7}{8}\rho_u} \tag{14}$$

For directions other than $\theta = 90°$ a more elaborate factor is required (Martin (122)). The turbidity also depends on the depolarization, and equations 6 and 8 for the turbidity must be multiplied on the right-hand side by the factor:

$$\frac{1 + \frac{1}{2}\rho_u}{1 - \frac{7}{8}\rho_u} \tag{15}$$

The derivations of these formulae are quite involved, and for a detailed treatment the reader is advised to see any of the numerous treatments of the subject (for example, Born (19), Gans (68), Stuart (201), and Bhagavantam (13)).

The depolarization of the scattered light may be determined visually by the Cornu method adapted by Cabannes (25). This method consists in dividing the scattered light into its horizontal and vertical polarized components with a double prism (Wollaston prism). The two components are then made to pass through an analyzer (nicol prism or polaroid); if the analyzer is rotated through the angle ϕ which makes the brightness of the two components equal, the depolarization is given by $\tan^2 \phi$ (see, for example, Woods (220, page 340)). For most systems the depolarization is small and the intensity of the horizontal component is difficult to measure visually except by the Cornu method. With the recent development and general availability of extremely sensitive photoelectric cells, particularly the photomultiplier cell, the depolarization can be measured directly by measuring photoelectrically the intensity of the scattered light when it passes through the analyzer with plane of polarization in the vertical and horizontal positions.

Cabannes (25) has discussed the conditions under which the depolarization can be accurately determined. They include the use of parallel light as the incident beam, the observations made exactly at 90° to the incident beam, and the elimination of dust which, as we shall see, can make a large contribution to the depolarization. Another precaution is the elimination of secondary scattering, whose contribution to the depolarization will be discussed later.

The maximum depolarization which can be theoretically obtained for a particle small compared with the wave length of incident light is that of scattered light from an infinitely thin rod. Then $\alpha_1 \neq 0$ and $\alpha_2 = \alpha_3 = 0$, so from equation 13 the depolarization is 0.5, and from equation 14 and 15, respectively, the intensity is 3.6 times and the turbidity 3.0 times that for isotropic particles of the same volume. For all the gases which have been measured, however, the depolarization is considerably less than one-half. Bhagavantum (13, pages 54 and 55) has compiled a table of the depolarization of seventy-six common gases and vapors. The values range from 0 for argon to 0.125 for nitrous oxide, corresponding to $\alpha_1 = \alpha_2 = \alpha_3$ for the former and $\alpha_1/\alpha_2 = \alpha_1/\alpha_3 = 2.61$ for the latter. The aromatic compounds show greater depolarization than do the corresponding aliphatic series, and the depolarization increases as one goes from ethane through ethylene to acetylene. If the molecules are highly optically active, the interpretation of the depolarization is difficult (Gans (63)). The depolarization of scattered light from liquids is complicated by the fact that the particles are not independent and the problem will be treated in detail later. For the very dilute solutions of proteins studied by Putzeys and Brosteaux (154) the depolarization was observed to be negligibly small (see Section II,B,4).

Under the influence of a strong electric field, most liquids and gases will exhibit a feeble birefringence. This phenomenon, called the Kerr effect after its discoverer (94), has been shown by Langevin (112) to be due, for anisotropic nonpolar gases, to the partial alignment of the molecules with their axes of greatest polarizability along the direction of the applied electric field. Langevin related the Kerr constant (the birefringence per unit field strength) to the polarizabilities of the molecules. Thus the depolarization can also be obtained from the Kerr effect (Raman and Krishnan (158)). The depolarization obtained from the scattered light and that calculated from the observed Kerr effect are in good agreement for non-polar anisotropic gas molecules, but for polar molecules the Kerr effect is largely due to the Debye orientation effect, and one must incorporate the theory of Born (18) for such molecules with assumptions concerning the angle which the permanent dipole makes with the axes of the polarizability ellipsoid (for review, see Stuart (201)).

B. LARGE PARTICLES

In the treatment given above we have considered the light scattered from small transparent particles as that of the radiation from an oscillating dipole. If, however, the particles possess a linear dimension greater than about one-tenth the wave length of the incident light, or if the particles are metallic, they cannot be considered optically small and the character of the light scattered is more complicated than that given by the dipole radiator theory of Rayleigh. For large particles the scattered light will be the superposition of the wavelets from various parts of the same particle. In the general case the phase and intensity of the wavelets will bear complicated relationships to each other. The solution of this problem is obtained by solving the boundary value problem of a plane wave incident upon a particle of arbitrary size, shape, orientation, and index of refraction. This general case has not been solved because of mathematical difficulties. For spheres, however, whether transparent or metallic, the problem has been solved by Mie (125), and important contributions have also been made by Debye (31) and by Rayleigh (175). Some attempts have been made to extend the Mie theory to other than spherical particles (see Gans (62) and Möglich (126)), but the problem is far from completely solved.

When the index of refraction of the particle is nearly that of the medium, then as will be shown, the problem reduces to that of calculating the phase relationships between the wavelets scattered from a fixed array of dipole oscillators making up the particle. The mathematical problem is then identical with that of the analogous x-ray-scattering case. Because of the mathematical simplicity of this problem, it is useful to separate this case from that of particles with arbitrarily high index of refraction. We shall also treat separately the special case of metallic particles, since metals have complex indices of refraction for the visible wave-length region of light.

1. *Large spheres*

Mie (125) (see also Debye (31) and Rayleigh (175)) obtained as a mathematical solution for the intensity of scattered light incident upon a sphere of arbitrary size and index of refraction a series expression in terms of spherical harmonics. The coefficients of the series are functions of the ratio, m, of the index of refraction of the particle and that of the medium and of the parameter $x = 2\pi R/\lambda'$, where R is the radius of the sphere and λ' is the wave length of the light in the medium. The series is the sum of the contributions to the scattering by the electric and magnetic multipoles of the oscillating electric charges.

For particles with radii comparable or large compared to the wave length of incident light, i.e., $x \geq 1$, and with index of refraction ratio, m, differing somewhat from unity, say, for example, $m \geq 1.3$, the calculations of the Mie series are lengthy, and for details the reader is referred to the original papers of Mie (125), Debye (31), and Rayleigh (175) and to the reviews by Epstein (50), Stratton (199, Chapter 9), and van der Hulst (211). The mathematical problem of the Mie theory is very similar to that of wave-mechanical collision processes in which the effective size of the particle is given in terms of the collision cross section and the wave length of the radiation is given in terms of the De Broglie wave length of the particles (see, for example, Mott and Massey (128, Chapter 2)).

In the case of very small spherical particles of finite index of refraction, i.e., for particles for which $mx \to 0$, Mie's theory reduces to the Rayleigh problem. For somewhat larger particles of finite index of refraction, say $m = 1.33$ and $x = 1$ (e.g., water droplets in air with radii about one-sixth the wave length of the incident light), the Mie series expression can be expressed with sufficient accuracy as the sum of terms involving the contributions to the scattering by the electric dipole and quadripole moments and the magnetic dipole moment. The intensities of the vertical and horizontal polarized components, i_1 and i_2, respectively, are given in this case by

$$\begin{aligned} i_1 &= \frac{\lambda'^2}{8\pi r^2}\left|\frac{a_1}{2} + \frac{(a_2 + p_1)}{2}\cos\theta\right|^2 \\ i_2 &= \frac{\lambda'^2}{8\pi r^2}\left|\frac{a_1}{2}\cos\theta + \frac{a_2}{2}\cos 2\theta + p_1\right|^2 \end{aligned} \tag{16}$$

Equations 16 refer to unpolarized incident light of unit intensity. a_1 and a_2 are the electric dipole and quadripole contributions, p_1 is the magnetic dipole contribution, and they are given by

$$a_1 = 2x^3\frac{m^2 - 1}{m^2 + 2} \qquad a_2 = -\frac{x^5}{6}\frac{m^2 - 1}{m^2 + 3/2} \qquad p_1 \simeq -\frac{x^5}{15}(m^2 - 1)$$

When the radius of the particle is small, only the electric dipole term, a_1, is important, and equation 16 reduces to the Rayleigh expression (equation 1) for the total intensity, $i_1 + i_2$, for unit intensity of unpolarized incident light: namely, to

$$i_1 + i_2 = \frac{\lambda'x^6}{8\pi^2 r^2}\left(\frac{m^2 - 1}{m^2 + 2}\right)^2(1 + \cos^2\theta) \tag{17}$$

where the polarizability, α, of the sphere is given by

$$\alpha = \frac{m^2 - 1}{m^2 + 2}\left(\frac{\lambda' x}{2\pi}\right)^3 = \frac{m^2 - 1}{m^2 + 2}R^3 \tag{18}$$

For larger particles than those to which equation 16 refers, the intensity will be given by an expression involving the contributions to the scattering by higher multipoles. Equation 16 shows that the scattering is not symmetrical about $\theta = 90°$, but that more light is scattered in the forward than in the backward directions. Furthermore, the light scattered at 90° is not perfectly plane polarized, although the particles are taken as being isotropic.

Debye (31) has obtained asymptotic expressions for the terms in the series of the form of equation 16, and several authors have calculated the series numerically for various-size particles with various indices of refraction.[2] For example, Shoulejkin (186) has calculated the Mie terms for spherical particles of index of refraction ratio $m = 1.33$ (applicable to, for example, water droplets in air, or, with a minor transformation, air bubbles in water) for x equal to 1, 3, and infinity. Blumer (17) and Caspersson (27) have computed the Mie terms for several values of m and x. Engelhard and Freiss (49), Paranjpe, Naik, and Vaidya (144), and Ruedy (181) have calculated the Mie terms for large values of x and have compared the calculated values of the angular dependence of scattering with those from artificial aerosols made by adiabatic expansions of vapors, as is done in a Wilson cloud chamber. The agreement of the observed results with those calculated constitutes a confirmation of the Mie theory.

In figure 3 are illustrated angular scattering diagrams from Blumer's calculations (17) for spheres for which $m = 1.25$ and x equals 0.8 and 4.0, respectively. For $x = 4.0$ the large area of forward scattering is not shown. As in figure 1, the dotted curves represent the intensity of the horizontal component of the scattered light and the smooth curves represent the intensity for the vertical polarized component. For both these cases more light is scattered in the forward directions than in the backward directions, in contrast to Rayleigh scattering (figure 1) which is symmetrical about 90°. The larger particle has a complicated scattering diagram which is typical of large particles, especially those with large index of refraction. The maxima and minima in the diagram increase in complexity as the size and index of refraction of the particle are increased and correspond to the increasing importance of the higher multipoles with their associated higher spherical harmonics in the Mie series. The complicated scattering diagram which is essentially the diffraction pattern of the large particles, reduces, in the limiting case of particles which are very large compared to the wave length of light, to the ordinary refraction and reflection diagram of geometrical optics together with the superimposed diffraction.

If white light is incident upon a monodispersed system of particles of large size and high index of refraction ratio, each color component of the white light will have its own complicated scattering pattern and the scattering system will exhibit vivid colors when viewed at various angles. Ruedy (181), for example, has examined the transmitted color and the colored rings about the transmitted beam of light in artificial fogs of water droplets. Keen and Porter (92) noted that sulfur sols exhibited changes in transmitted colors as the sols aged, that is, as the particles increased in size. Ray (171) (see also Raman and Ray (165)) found that sulfur sols exhibited a few orders of colors when viewed at various angles with respect to the incident beam. A detailed study of this phenomenon has recently been carried out by La Mer and his coworkers. La Mer and Barnes (107) made a special effort to obtain monodispersed sulfur sols and were able to see as high as nine orders of colors in angular scattering. It is necessary to obtain nearly monodispersed systems, since a mixture of particles of various sizes will not give distinct color bands. Johnson and La Mer (91a) have shown that as the monodispersity is increased the color bands become more distinct, and propose that this effect may be used as a test of homogeneity of the size of the particles. They have measured the position and ratio of the intensities of the red to green colors of sulfur sols of known particle sizes and obtained good agreement with the Mie theory. It should be remembered, however, that sulfur has a high index of refraction ($m \simeq 1.5$ in water) and for particles of low refractive index of refraction, say, for example, protein material ($m \simeq 1.15$ in water), in order to exhibit colors the particles must be so large that they can easily be seen in a light microscope. Nevertheless, for large-size protein-containing substances such as blood cells or bacteria, small changes in size due to drying can be easily followed by studying changes in the angular color pattern or diffraction pattern of suspensions of these particles (for review, see Ponder (152)).

---

[2] *Added in proof:* The most complete calculations to date are those carried out by A. Lowan and his associates. They are available from the U. S. Department of Commerce Office of Publications Board, Washington, D. C.

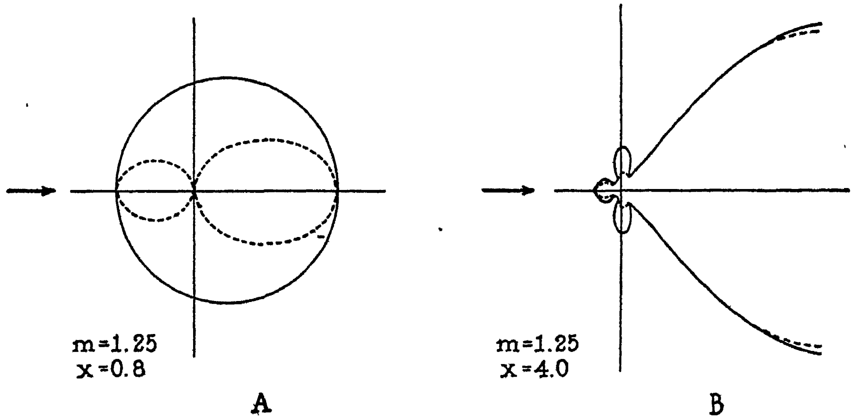


FIG. 3. Angular scattering diagrams for spheres (from calculations by Blumer (17))

In order to calculate the turbidity or extinction coefficient for a scattering system, it is necessary to integrate the intensity of scattered light over all angles. Rayleigh scattering gives a symmetrical angular pattern and the integration is easy to perform. For larger particles, however, the angular distribution is given by the Mie series, and the integration is difficult to perform. Jobst (91) obtained an approximate value for the sum of the Mie series by utilizing the asymptotic expressions for the terms in the series obtained by Debye (31). While for small particles the extinction coefficient is proportional to the sixth power of the radius and inversely proportional to the fourth power of the wave length of incident light, Jobst finds, for particles comparable to the wave length of light, that the extinction coefficient is proportional to the fourth power of the radius and inversely proportional to the square of the wave length. For very large particles, the extinction coefficient is proportional to the square of the radius and is independent of the wave length. Since the extinction coefficient or turbidity becomes less dependent on wave length as the particles are increased in size, a system of large particles will, when illuminated with white light, appear whitish when viewed at 90° instead of bluish as for Rayleigh scattering. An estimation of the size of particles can be made by determining spectrophotometrically the dependence of the turbidity on the inverse power of the wave length (see Heller, Klevens, and Oppenheimer (85), Heller and Vassy (86), and Doty (42)).

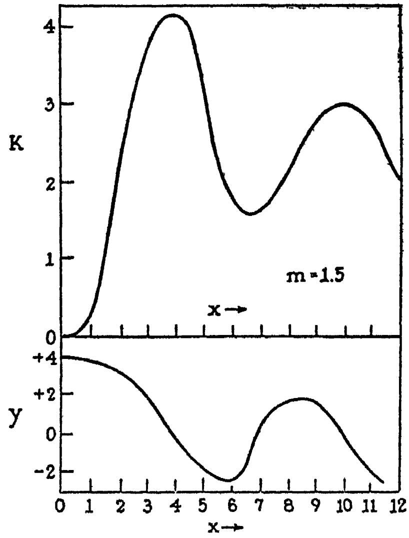


FIG. 4. Upper: extinction coefficient per cross-sectional area as a function of size of sphere. Lower: power of x/λ as a function of size of sphere (La Mer (106)).

For the purposes of this discussion it is convenient to consider the scattering area coefficient, K, which is the extinction coefficient per cross-sectional area of the particle and which may be written quite generally as:

$$K = Q\left(\frac{x}{\lambda}\right)^{y} \tag{19}$$

Q is a function of m, and y varies from 4 for a Rayleigh scatterer to 0 for a particle large compared to the wave length. For some intermediate particle sizes y can be negative as may be seen in figure 4, calculated by La Mer (106) from the Mie theory. Figure 4 and similar curves by Stratton and Houghton (198), by van der Hulst (211), and by Sinclair (187) show that the extinction coefficient per cross section increases in the Rayleigh region as x^4 and reaches a maximum of from about 3 to 5, depending on the value of m, while for large x it oscillates with diminishing amplitude about the value 2 as x increases. That is, as the geometrical optical region is approached, the extinction becomes equal to twice the cross-sectional area of the particle. This result, which follows from computations of the higher Mie terms for very large particles, appears to be twice as great as one would expect from geometrical optics, to which the Mie theory must reduce for very large particles. This apparent paradox has been explained in detail by van der Hulst (211, Chapter 5; see also Sinclair (187)), who showed that even in geometrical optics a sphere will extinguish twice the amount of light striking it. Half this amount of light is scattered in a narrow peak of only slightly deviating rays on the exit beam. If the incident plane wave comes from a distant source and if the observation is made at a sufficiently great distance from the particle, the extinction will be twice the cross-sectional area of the particle. In the usual experiments in geometrical optics, however, the particle may be of macroscopic dimensions and the light source and observer are not at sufficiently great distances to observe this phenomenon. An example of the large distances required is given in the transmission experiments of Sinclair (187) with lycopodium spores (radius equal to 15 microns). At an observation distance of 6 in. from the spores the extinction coefficient was found to be equal to the cross-sectional area and only at a distance of 18 feet or greater was the extinction coefficient equal to twice the cross-sectional area. The applications of the theory of turbidity of large spherical particles are very important to the problem of visibility in astronomy and meteorology and the reader is referred to the book of Middleton (124), which contains a few hundred references on this problem.

As indicated earlier, the turbidity is less dependent on the size of the particle for very large particles than for small ones. For a given weight (or volume) of material which is monodispersed into particles of very small size so that Rayleigh's law is obeyed, the turbidity will increase as the third power of the radius, since the number of particles per unit volume of the system decreases inversely as the third power of the radius, while the scattering of each particle increases as the sixth power of the radius, and the turbidity is the product of these quantities. When the particles are comparable in size to the wave length of incident light, the scattering per particle is proportional to the fourth power of the radius, and the scattering for a given weight of material will increase linearly with the radius. For still bigger particles the scattering is proportional to the square of the radius, so that the scattering of the system will actually decrease with increasing radius of the particles. Thus, maximum scattering will occur for a given weight of material when the particles are about equal in size to the wave length (i.e., when the particles have a diameter nearly equal to the resolving power of the light). In figure 5 are shown curves for the dependence of the extinction coefficient of a given weight of material on the particle diameter. The data are taken from the work of Caspersson (27), who calculated them from the Mie theory. Note that the particle size for which the maxima occur is independent of the refractive index ratio. The position does depend, however, on the index of refraction of the medium, which determines the resolving power. Paint manufacturers have learned by experience that the maximum spreading power of colorless material is achieved by grinding the material to a size corresponding to the resolving power of the light. Clewell (29) (see also Barnett (10), Andreason (3), Bailey (7), and de Vore and Pfund (38)) has examined suspensions of highly refracting substances and found the maximum in turbidity given in figure 5. The curves also show that for certain sizes (in figure 5, particles with a diameter of 380 mμ) the longer wave length will be scattered more than the shorter one, a result which is the reverse of that in Rayleigh scattering.

2. Metallic particles

The vivid colors exhibited by metal sols are due mainly to selective absorption of the light by the metals. For sufficiently large particles, however, scattering can also play a rôle in determining the color of the sol. The color phenomena of metal sols are described in detail by Wo. Ostwald (143), by Svedberg (204, page 193 *et seq.*), and by Freundlich (57, Volume 2, page 26 *et seq.*), who also give extensive bibliographies.

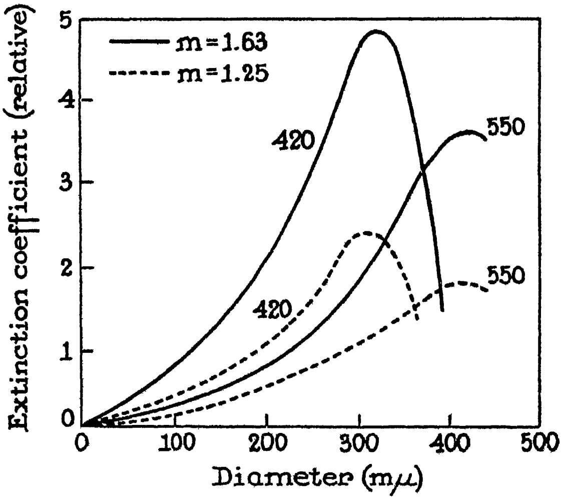


FIG. 5. Relative extinction coefficient as a function of diameter of spheres for constant weight concentration of scattering material (from calculations by Caspersson (27)).

According to Mie (125), the color of metal sols may be deduced from his theory when the index of refraction of the metal, n', is given in complex form

$$n' = n - ik \tag{20}$$

where n is the ordinary index of refraction and $4\pi k/\lambda$ is the absorption coefficient of the metal. For all metals in the visible region of the spectrum, n and k are nearly equal and are of the order of unity. Both quantities vary considerably with the wave length in a manner characteristic for each metal (see, for example, Mott and Jones (129, Chapter 3, sections 7 and 8). At long wave lengths (infrared wave lengths or greater) n and k are equal and are large compared to unity. For such long wave lengths there is considerable reflection of the incident light in the backward directions.

Steubing (196) examined the transmission and the 90° scattering of gold sols in some detail. He found that sols of small particle size (radius about 25 mμ) strongly absorbed green light and thus appeared red on transmission and showed very little scattering. For larger particles, the absorption band is broader and shifts toward the red and there is considerable right-angle scattering. Such sols appear blue on transmission. Mie (125) showed that the phenomena reported by Steubing are explainable in a quantitative fashion by his theory.

For each metallic sol the absorption coefficient and index of refraction of the metal as a function of wave length must be known in order to explain the color of the sol. Further complications are introduced if the metallic particles are not spherical (see Gans (61)) or homogeneous in size. The polarization of scattered light from metallic spheres is similar to that expected for transparent spheres.

The theory of the light scattering from metallic particles has been used in the study of the transmission of light through interstellar space. Recent work indicates that much of the matter in interstellar space is in the form of particles comparable in size to the wave length of light. From an analysis of the absorption coefficient, estimates can be made of the distribution of these particles in interstellar space (the work up to 1940 has been summarized by Schoenberg and Lambrecht (185)).

3. *Particles with relative index of refraction near unity*

Particles which are comparable in size to the wave length of incident light and which possess a high relative index of refraction exhibit a complicated scattering pattern. This pattern, given by the Mie series, is determined not only by the interferences between the wavelets scattered by the volume elements of the same particle, but also by the distortions in phases and electric field associated with the incident and outgoing light brought about by the electromagnetic interactions of the field and the polarizable scattering elements. As indicated above, even for such a simple shape as a sphere, the solution of the problem is quite complicated. For particles with relative index of refraction m near unity, however, the distortion effect on the primary and scattered waves is small; and, to a first approximation, only the relative phases of the wavelets from the scattering elements, treated as dipole oscillators, need be considered. The relative phase relationships of the wavelets from various parts of the same particle are determined by the relative positions of the scattering elements, that is, by the shape of the particle, and therefore the problem is identical mathematically with the analogous problem in x-ray and electron scattering by molecules.

The treatment of the scattering of large particles as that of an assembly of independent dipole oscillators will be valid if the condition $2x(m - 1) << 1$ is satisfied. Thus for particles, such as bacteria in water, which have a low relative refractive index but are large compared with the wave length of light, this simplified picture will not apply. In general, however, chemists are interested in particles which are too small to be seen in the light microscope. For protein less than 1.2; and since these particles possess a linear dimension equal to or less than the wave length of light, the simplified treatment is applicable. In cases where the index of refraction of the particle is quite high, the relative index of refraction can be reduced by dissolving some highly refractive substance into the suspending medium.

For a particle with a dimension equal to the wave length of light or greater than it and having a relative index of refraction nearly unity, each volume element of the particle will scatter light according to the Rayleigh relation given by equation 1. The wavelets will interfere, because the phase relationships between the wavelets coming from the various volume elements of the same particle are fixed. There will be more light scattered in the forward directions than in the backward directions, since wavelets from particles along the incident beam will be approximately in phase, but in the backward direction they will generally be out of phase with some destructive interference and a consequent loss in intensity. The radiation envelope will be smooth, as for the particle in figure 3A, and the larger the particle the greater will be the forward scattering. The $1 + \cos^2 \theta$ factor of Rayleigh scattering of unpolarized incident light is symmetrical about 90° to the incident beam and can be omitted from the discussion, since we shall consider observations made at angles symmetrical about this direction. As P. Debye (32) and P. P. Debye (36) have pointed out, intensity measurements made at two equal angles on either side of 90° define the shape of the radiation envelope and allow for a determination of the size of the scattering particle. The ratio of the intensity of light scattered in some forward angle ($\theta < 90°$) to that scattered at its supplementary angle, $180° - \theta$, is called the dissymmetry of the scattering system. We shall now consider the dependence of dissymmetry on the size of the particle for three types of particles frequently encountered in high-polymer chemistry,—namely, for spheres, random coils, and rods.

Just as for x-ray and electron scattering, the intensity of light scattered from an assembly of light-scattering elements making up the particle is proportional to

$$\sum_i \sum_j \frac{\sin\left(\dfrac{4\pi r_{ij}}{\lambda'} \sin \dfrac{\theta}{2}\right)}{\dfrac{4\pi r_{ij}}{\lambda'} \sin \dfrac{\theta}{2}} \tag{21}$$

where λ' is the wave length of light in the medium and r_{ij} is the distance between the elements i and j. This formula may be expressed in integral form in terms of the vector distance separating two volume elements and the density of pairs of such elements. This latter function—the radial density—is determined by the arrangement of the scattering elements, that is, by the shape of the large particle. Equation 21 and its integral representation are derived in detail in most treatments of x-ray and electron scattering by molecules (see, for example, Compton and Allison (30, Chapter 3) and Pirenne (149, Chapter 7)).

For spherical particles the scattering elements are spherically symmetrically distributed. The radial density function is a constant for such an arrangement of scattering centers. The integral representation of equation 21 for a sphere of diameter L leads to the following expression for the angular dependence of the scattered light intensity when normalized (intensity is unity for $\theta = 0$)

$$\left[\frac{3}{z^3}(\sin z - z\cos z)\right]^2$$

where

$$z = \frac{2\pi L}{\lambda'}\sin\frac{\theta}{2} \tag{22}$$

This formula was first derived by Rayleigh (176) (see also Gans (65)) and is identical with that obtained by Landshoff (108) for light scattering from spherical aggregates of small particles. The same expression was obtained by Debye and Menke (35) in their study of the x-ray diffraction of liquid mercury. For x-ray scattering by liquids this term has importance only for angles extremely close to the main beam and is, therefore, neglected in most x-ray studies. This small angle scattering of x-rays is important, however, in the case of finely divided powders; and for carbon black the size of the clusters of the tiny particles can be determined by equation 22 from the angular distribution of the radiation scattered at small angles (Biscoe and Warren (16)). The Mie theory reduces to the same result as equation 22 for spherical particles which have sufficiently small relative index of refraction and size (van der Hulst (211, Chapter 4). In figure 6 is illustrated (P. P. Debye (37)) the expression of equation 22 as a function of angle for spheres of various sizes. Incidentally, equation 22 is expressible by the Bessel function of the 3/2 order, $J_{3/2}(z)$, and is equal to

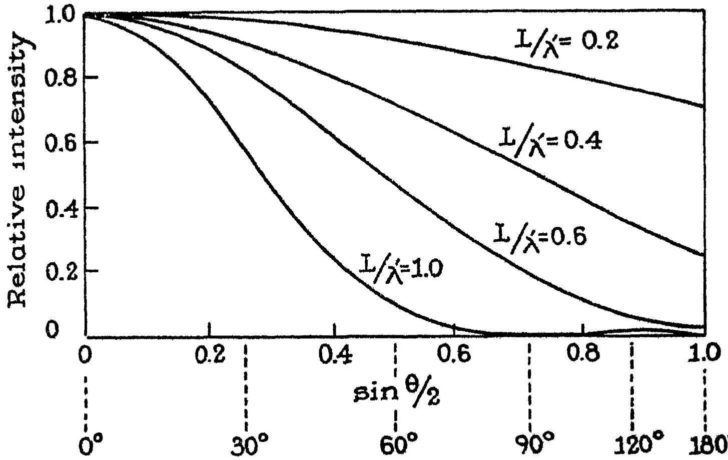


FIG. 6. Relative intensity of scattering as a function of angle for spheres of low relative index of refraction (P. P. Debye (37)).

$$\frac{9\pi}{2z^3}J^2_{3/2}(z)$$

Tables for this Bessel function are available.[3] As can be seen from the curves, the intensity of scattering is greater in the forward directions than in the backward directions. The curves show that for these particles the radiation envelopes are smooth and that only for the comparatively large sphere $L = \lambda'$ at an angle close to the main beam is there any deviation from a simple behavior. In figure 7 is illustrated the ratio of the intensities of the scattered light for observations made at 45° on either side of 90° to the incident beam. The dissymmetry rises very rapidly with increase in particle diameter.

The dissymmetry for spheres may be illustrated by the results obtained for influenza virus by the reviewer. Measurements were made at 45° and 135° in a light-scattering photometer developed by Speiser and Brice (193).[4] The apparatus consists essentially of a mercury lamp with monochromatic filters, a lens for projecting a narrow beam through the center of the scattering cell, a sensitive phototube mounted on an arm capable of rotation about a vertical axis, and a removable polarizer and analyzer for determining depolarization. If a rectangular cell is used, it is necessary to correct the angles for refraction at the solution–glass–air interfaces (Debye (36); see also Stein and Doty (194)). Such a correction may be eliminated by using a cell whose faces are normal to the outgoing scattered beam. A spherical cell with radius large compared to the

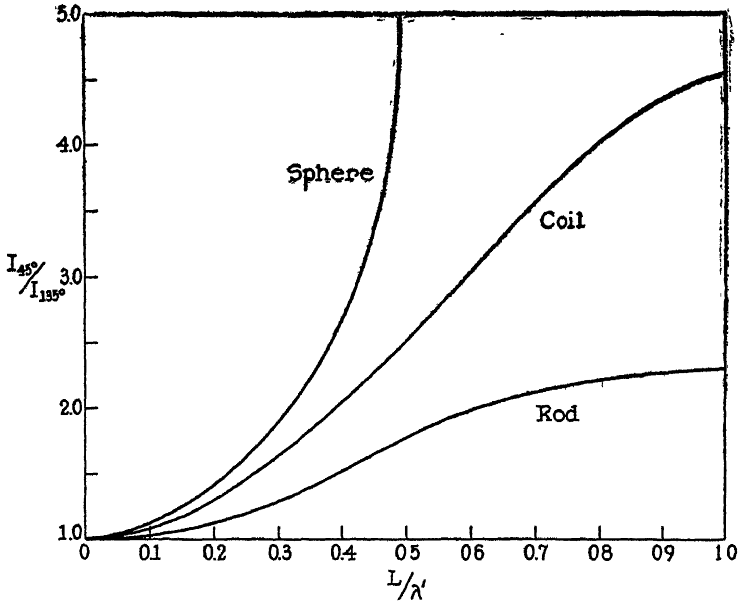


FIG. 7. Dissymmetry as a function of L/λ' for spheres, coils, and rods of low relative index of refraction.

---

[3] *Tables of Spherical Bessel Functions*, Vol. I. Columbia University Press, New York (1947).

[4] The author is indebted to Dr. B. A. Brice of the Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia, Pennsylvania, for the use of this apparatus.

cross-sectional area of the scattered beam has been found satisfactory by the reviewer. By introducing a mirror which can be rotated in a rectangular cell P. P. Debye (36, 37) insures that the scattered light is always normal to the face of the cell so that no correction need be made in the angles. The results for the scattering of blue light from a solution of a highly purified sample of influenza virus (PR8 strain) in 1 N phosphate buffer at pH 7 are shown in figure 8. On extrapolating to infinite dilution the dissymmetry is found to be equal to 2.6. This dissymmetry corresponds in figure 7 to a ratio of diameter to wave length of 0.39; and since the blue light was obtained with a filter having a maximum transmission at 436 mμ, the diameter of the particles is calculated to be (0.39)(436)/1.33 or 128 mμ. This value is 28 per cent higher than that obtained from spectrophotometric measurements of the turbidity (Oster (138)). The discrepancy in values obtained by the two methods may be due to the fact that, since the blue filter allows some light of wave lengths shorter than 436 mμ to be transmitted and since the dissymmetry for spheres of this size range rises rapidly with a slight decrease in wave length, the observed dissymmetry is higher than that which might be obtained if purely monochromatic light had been employed. Because of the high sensitivity of dissymmetry to particle size the dissymmetry method may be conveniently employed to study the swelling of spheres. Molecules which clump together to give spheres of these sizes show large dissymmetry; and Doty, Wagner, and Singer (45) have studied the association of polyvinyl chloride in dioxane by this method (see also Landshoff (108)).

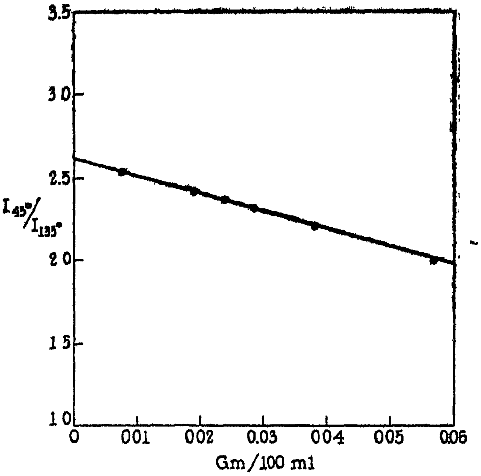


FIG. 8. Dissymmetry (λ = 436 mμ) of aqueous solutions of the PR8 strain of influenza virus.

For randomly coiled polymers the radial density function is given by the Gaussian distribution employed by Kuhn (104); namely, by

$$\left(\frac{3}{2\pi L^2}\right)^{3/2} e^{-3/2(r^2/L^2)} \qquad (23)$$

L is the root mean square distance between the ends of the polymer and is given in terms of the number of links in the polymer chain, s; each link is of length l and can rotate freely, making an angle ϕ with its nearest neighbors. The mean square distance between the ends is given by Kuhn as:

$$L^2 = sl^2 \frac{1 + \cos \phi}{1 - \cos \phi} \tag{24}$$

When the links are not able to rotate freely with respect to one another, more elaborate expressions in terms of the energy of the hindered rotation barrier may be used (Bresler and Frenkel (21), Sadron (182), and Taylor (204a)). When the radial density function of equation 23 is substituted into the integral representation of equation 21, the intensity when normalized (intensity is unity for $\theta = 0$) becomes,

$$\frac{2}{t^2}\left[e^{-t} - (1 - t)\right] \tag{25}$$

where

$$t = \frac{2}{3}\left(\frac{2\pi L}{\lambda'} \sin \frac{\theta}{2}\right)^2$$

This formula, first obtained by Debye (32), is derived in detail in the paper by Zimm, Stein, and Doty (225). In figure 7 the dissymmetry for θ equal to 45° and 135° is given as a function of the ratio of L to the wave length of light in the medium. The degree of coiling of a polymer chain can conveniently be determined by studying the deviations of the dissymmetry from that given by equation 25. Thus, P. P. Debye (37) found that latex particles gave a higher dissymmetry than that expected for randomly coiled chains. The particles are tightly coiled and give a dissymmetry calculated for spheres. Stein and Doty (194), on the other hand, found that cellulose acetate molecules with a molecular weight below 80,000 exhibited in acetone less dissymmetry than that calculated for a random coil and gave values closer to that expected for a rigid rod (see below). The cellulose acetate molecules of higher molecular weights show dissymmetry corresponding to a more kinked condition. It is seen that the dissymmetry method provides a means for studying changes in the shape of high-polymeric molecules in solution. Such changes can be brought about by variations of the type of solvent or variation of the temperature and can be followed as a function of time. The dissymmetry studies of Doty, Affens, and Zimm (43) on polystyrene show that these molecules are in the randomly coiled state in solution. In their measurements, the authors of these latter two papers obtained accurate results with an extraordinarily simple dissymmetry apparatus developed by them. Light scattered at two equal angles on either side of 90° was reflected from mirrors into a comparator photometer and the two light beams were equalized visually.

A thin stiff rod of low relative refractive index may be regarded as a linear array of dipole scatterers. The normalized intensity for a thin rod of length L is given by

$$\frac{1}{z}\int_0^{2z} \frac{\sin w}{w}\,dw - \left(\frac{\sin z}{z}\right)^2 \tag{26}$$

where

$$z = \frac{2\pi L}{\lambda'} \sin \frac{\theta}{2}$$

This formula was derived independently by Neugebauer (134) and by Debye (32). A detailed derivation is also given in the paper by Zimm, Stein, and Doty (225). The definite integral (w is a variable over which the integration is taken) in equation 26, called $Si\ (2z)$ in the mathematical literature, is given as a function of $2z$ in certain tables of special functions.[5] Oster, Doty, and Zimm (142) give values for the dissymmetry as a function of angle for various rod length to wave length ratios. In figure 7 the dissymmetry at θ equal to 45° and 135° is given as a function of the ratio of the length of the rod to the wave length in the medium. The dissymmetry for rods is less than for spheres or coils of comparable size. For particle lengths of the size of the wave length or greater, the dissymmetry increases relatively slowly with increase in particle length. To study particles of such great lengths, the intensities at angles closer to the main beam of light should be measured. However, if angles too close to the main beam are chosen, there is a danger of picking up stray scattered light. In figure 9 is shown the angular distribution of scattered light as measured in the apparatus of Speiser and Brice (193) for two dilute solutions of tobacco mosaic virus particles. Figure 9A shows the relative intensity of light (λ = 546 mμ) scattered at angles from 45° to 135° in 5° intervals for a sample which had been rendered nearly biologically inactive by having been subjected to very strong sound irradiation for 64 min. This sample has been shown (Oster (140)) by direct examination in the electron microscope to consist of rod-like particles of one-half the length of normal biologically active virus or shorter. The angular scattering of the normal particles is given in figure 9B. From figure 9 the dissymmetry at 45° and 135° is 1.20 and 2.06 for the shorter and longer particles, respectively. From figure 7 the average length of the particles is calculated to be 103 mμ and 275 mμ. The type of average for a system of many particle lengths which the dissymmetry determines depends on the length of the particles for, as seen in figure 7, particles of very great length do not show a dissymmetry much greater than shorter particles which are still great in length. In the intermediate regions, however, for L/λ' from about 0.3 to 0.6, the dissymmetry increases approximately linearly with the length of the particles, so that the dissymmetry for a polydispersed sample of rods of lengths lying in this range will be determined by the mean length of the particles. It should be emphasized that the particle-length region where the dissymmetry is approximately linear with the length of the particles depends on the scattering angles which one chooses. As seen in figure 9A, the angular light scattering for the shorter particles is nearly symmetrical with a minimum near 90°. For unpolarized incident light the curve for a single dipole scatterer is given by $1 + \cos^2 \theta$, and figure 9A is this curve with a slight forward dissymmetry superimposed on it. The virus particles of normal size, however, show a strong forward scattering. The particle length calculated for the dissymmetry at 45° and 135° is in good agreement with that found by Oster, Doty, and Zimm (142), who studied the dissymmetry of a similar sample at two different angles in the visual photometer described earlier. These authors determined the particle length by viscosity and electron microscope studies and obtained close agreement with that determined by the dissymmetry method with the same sample. The reviewer (141) has been able to determine by the dissymmetry method the particle length of long rods of tobacco mosaic virus particles which have been made to aggregate end-to-end and which exceed 1

---

[5] See, for example, The British Association for the Advancement of Science, *Mathematical Tables*, Vol. I, London (1931).

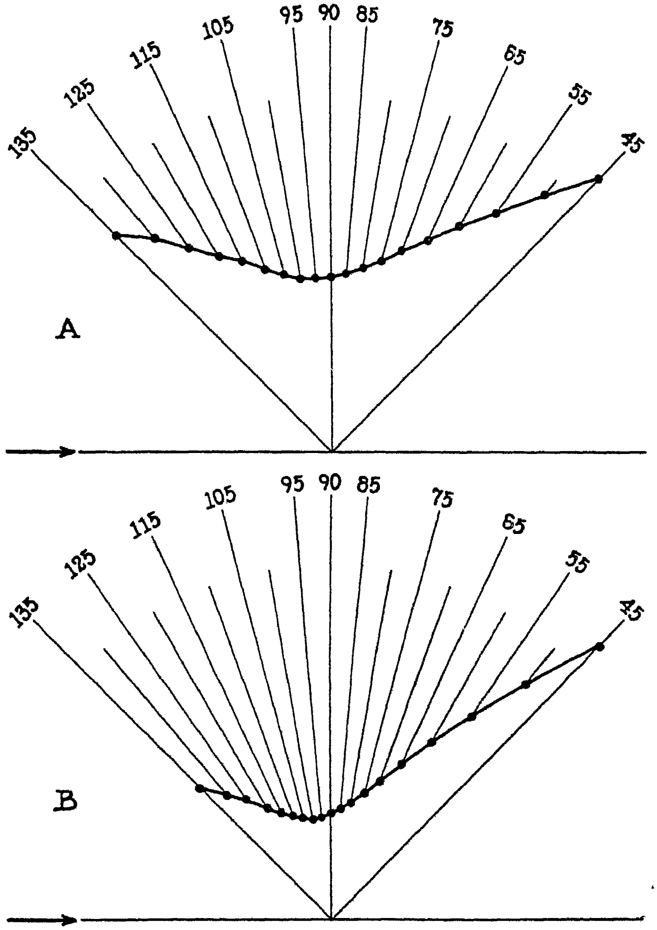


FIG. 9. Angular scattering ($\lambda = 546$ mμ) for solutions (protein concentration of 0.01 g./100 ml. buffered at pH 7.0) of (A) tobacco mosaic virus which had been subjected to sonic irradiation for 64 min. and (B) normal freshly purified tobacco mosaic virus.

micron in length. This method should prove of value for studying the end-to-end aggregation of other fibres, particularly those encountered so frequently in biology. The dissymmetry method is perhaps superior to stream birefringence and viscosity methods for determining the lengths of elongated particles, since it determines the length of the particles as they exist in solution under equilibrium conditions. The latter two methods, however, involve subjection of the particles to a shear gradient in order to make them flow; and this process can in some cases distort the normal shape of the particles (Kuhn (105), Frenkel (55)). Doty (42) has integrated numerically the angular scattering curves for rods of several lengths. From these results he is able to determine the particle length of rods from the dependence of the turbidity on wave length as determined in a spectrophotometer. This method is similar to that described for spheres in the previous section.

From figure 7 it appears that the dissymmetry for rods or coils approaches limiting values as L/λ' increases. If the dissymmetry is determined at two angles symmetrical about 90°, then it may be shown from equation 26 that for rods the dissymmetry approaches cot $\theta/2$ for large values of L/λ' (note that $Si\ (2z) \rightarrow \pi/2$ and $(\sin z/z) \rightarrow 0$ for large z). Similarly it may be shown that for coils the dissymmetry approaches $\cot^2 \theta/2$ and for spheres the dissymmetry oscillates about $\cot^4 \theta/2$ for large values of L/λ'. Since the dissymmetries for rods, coils, and spheres approach quite different values, the general shape of the particle can be determined from the limiting value of the dissymmetry.[6] Stein (195) has suggested that the limiting value of the dissymmetry could be determined by measuring the dissymmetry for continuously decreasing wave lengths (and therefore increasing values of L/λ'), using a variable monochrometer as a light source.

The molecular weight of spheres of known density can be found from the dissymmetry, since this method determines the diameter of the particles. For coils and rods, however, only the length of the long dimension is determined, so that another measurement must be made in order to find the molecular weight of the particles. Because of the destructive interference among the wavelets scattered from particles comparable in size to the wave length of light, the turbidity will be less, per unit volume of scattering material, for such large particles than for very small particles. In making molecular weight determinations of such large particles the turbidity must be corrected by a factor greater than unity to account for this decrease in scattering. If the turbidity is determined in the transverse direction, it must be multiplied by the reciprocal of relative intensity given by equations 22, 25, or 26, depending on the shape of the particle, for $\theta = 90°$ and L/λ' determined by the dissymmetry measurement. This corrected value for the turbidity, for sufficiently dilute solutions, gives from equation 10 the molecular weight of the particles. By applying this correction, determined graphically from the dissymmetry measurements, to their measurements of the turbidity of solutions of tobacco mosaic virus, Oster, Doty, and Zimm (142) obtained a molecular weight for these particles which agreed closely with that obtained from other methods.

---

[6] *Added in proof:* These ideas have recently been utilized by W. K. Jordan and G. Oster (Science **108**, 188 (1948)) in their light-scattering studies of changes in shape of the very long fibrillar muscle protein, actomyosin.

The dissymmetry of a system of particles is very sensitive to particle interactions. Thus Oster, Doty, and Zimm (142) found that the dissymmetry of scattering from very dilute solutions of tobacco mosaic virus in water decreased markedly with increase in virus concentration. In buffer at pH 7.0, however, the dissymmetry was found to be independent of concentration in this low concentration region. The reviewer has investigated this system further (141) and has found that for much higher virus concentrations the dissymmetry of solutions of the virus in the buffer at pH 7.0 also decreased with increasing virus concentration, but that the solutions of the virus in water show a much steeper decrease and beyond a certain concentration show an increase in dissymmetry with concentration. The concentration for the minimum in dissymmetry is correlated with a maximum in turbidity and with the formation of the liquid crystalline state (see reference 141 for details). Zimm (223) has developed an approximate theory which attempts to correlate the concentration dependence of the dissymmetry with certain thermodynamic quantities which express the extent of the deviation of the solution from ideality. This problem will be discussed later in this review when non-independent particle systems are considered. There can be, however, a decrease in dissymmetry with concentration which is not due to particle interactions. The reviewer (141) has studied the dissymmetry of solutions of tobacco mosaic virus as a function of virus concentration for two wave lengths. When extrapolated to infinite dilution the curve for the shorter wave length ($\lambda = 436$ mμ) gives a higher dissymmetry than that for the longer wave length ($\lambda = 546$ mμ) and both correspond from figure 7 to that for a rod 275 mμ in length. For concentrations above 0.03 per cent, however, there is a reversal in relative values of the dissymmetries. The dissymmetry measured with the blue light now becomes less than that for the green light, and the difference between the dissymmetries for the two colors becomes more pronounced as the concentration of the virus is increased. This anomalous behavior may be due to several causes which depend on the geometrical arrangement, size, and convergence of the incident beam of light and on the turbidity of the sample. This problem will be considered in detail in the discussion of anomalous depolarization given below. In general, it is difficult to correct for these effects; and for most systems the dissymmetry is easily interpretable only when it is extrapolated to infinite dilution, as is done for influenza virus in figure 8.

4. Depolarization by large particles

The character of the polarization of the light scattered by a system of particles is determined by the size and the optical anisotropy of the particles. As discussed earlier, small isotropic particles exhibit complete vertically polarized scattered light at 90°, while small anisotropic particles show some depolarization in this direction. Spherical particles which are comparable in size to the wave length of light also exhibit depolarization, although these particles may not be anisotropic. Thus, depolarization studies enable one to determine the size range and anisotropy of the scattering particles.

The intensities of the horizontal and vertical components of the light scattered at 90° are usually denoted by H and V, respectively. The subscripts u, h, and v denote unpolarized, horizontally polarized, and vertically polarized incident light, respectively. In terms of the quantities V_v, H_v, V_h, and H_h, the depolarizations are given by

$$\rho_v = \frac{H_v}{V_v} \tag{27a}$$

$$\rho_h = \frac{V_h}{H_h} \tag{27b}$$

$$\rho_u = \frac{H_h + H_v}{V_h + V_v} = \frac{H_u}{V_u} \tag{27c}$$

Some authors define ρ_h as the reciprocal of that given in expression 27b—namely, by H_h/V_h—and this is occasionally a source of confusion. The components for four types of scattering particles—small isotropic, small anisotropic, large isotropic spheres, and large anisotropic non-spherical particles—will now be considered.

Optically isotropic particles which are small enough to show Rayleigh scattering give a scattering diagram exhibited by a dipole oscillator. This diagram (figure 1) shows that if the incident light is horizontally polarized, the intensity of light scattered at 90° is zero. If the incident light is vertically polarized, all the light scattered at 90° is vertically polarized. This condition is expressed by

$$V_v \neq 0 \quad H_v = V_h = H_h = 0 \quad \rho_v = 0 \quad \rho_h = 1 \quad \rho_u = 0 \tag{28}$$

Small anisotropic particles, however, exhibit depolarization at 90° when the incident light is either vertically polarized or is unpolarized. For these particles, the plane of polarization of the incident light may not lie in the direction of the induced moment and, as can be shown (see Gans (68)), give rise to the following values for the components:

$$V_v \neq H_v = V_h = H_h \neq 0 \quad \rho_v \neq 0 \quad \rho_h = 1 \quad \rho_u \neq 0 \tag{29}$$

Large isotropic spherical particles should, according to Mie (125), exhibit depolarization at 90°. As the particle size is increased the terms corresponding to the higher electric and magnetic multipoles increase in importance (see equation 16), with a resultant increase in ρ_u. Blumer (17) has calculated the depolarization, ρ_u, for spheres of various sizes and indices of refraction, and the theory has been confirmed by the light-scattering studies of Pokrowski (151) and Lange (111) with colloidal solutions and of van dem Borne (210) with aerosols. The components of the light scattered at 90° for large spherical isotropic particles are given by

$$V_v \neq 0 \quad H_v = V_h = 0 \quad H_h \neq 0 \quad \rho_v = 0 \quad \rho_h = 0 \quad \rho_u \neq 0 \tag{30}$$

The depolarization of light scattered from large anisotropic particles has been calculated by Gans (62). The components for such particles are the superposition of those for the small anisotropic and for the large isotropic particles, or

$$V_v \neq 0 \quad H_v = V_h \neq 0 \quad H_v \neq 0 \quad \rho_v \neq 0 \quad \rho_h \neq 0 \quad \rho_u \neq 0 \tag{31}$$

In all four cases the relation $H_v = V_h$ holds. This is a statement of the reciprocity theorem of optics due to Rayleigh (174) and was found by experiment to be valid for light-scattering systems by Krishnan (97). Perrin (146) has examined the theorem in great detail for light-scattering systems and concludes that the relation is valid for a system of a large number of particles which have no preferred orientation in space. The reciprocity theorem together with equation 27c gives the important relation due to Krishnan (97):

$$\rho_u = \frac{1 + \dfrac{1}{\rho_h}}{1 + \dfrac{1}{\rho_v}} \tag{32}$$

Thus if two of the depolarizations are known, the third may be calculated. This is particularly important in the determination of ρ_h, which is often difficult to measure directly. The Krishnan relation (equation 32) has been confirmed by several investigators with various scattering systems (Krishnan (100), Mueller (132), Boutaric and Breton (20), Hoover, Putnam, and Wittenberg (88), Subbaramaija (202), Ramaiah (156), Gehman and Field (70)).

As seen in equations 28, 29, 30, and 31, a system of isotropic particles irrespective of size gives $\rho_v = 0$ and if the particles are anisotropic, then $0 < \rho_v < 1$. For random coils containing anisotropic segments the net anisotropy of the coils is decreased as the number of segments is increased (Neugebauer (134), Strauss (200), and Kuhn (103)). For small particles irrespective of anisotropy and shape $\rho_h = 1$, but when the particles are comparable in size to the wave length of light and are isotropic $\rho_h < 1$. In the special case of thin rods which are comparable in length to the wave length of light and whose index of refraction along the long axis differs from that perpendicular to it, Gans (69) (compare Vrkljan and Katalinis (216)) calculates that $\rho_h > 1$ (see, however, the recent review by Doty (41)).

The depolarizations can be conveniently determined by the Cornu method described earlier. Another method, due to Krishnan (98), employs two Wollaston prisms. The first divides the incident beam of light into its horizontal and vertical polarized components. The second prism placed at right angles to the scattering cell divides the two scattered beams into the four polarized components V_v, H_v, V_h, and H_h, which may be photographed and compared in intensity (for a detailed discussion of errors of measurement, see Volkmann (215)). Raman (157) has proposed the use of the Babinet compensator (for a general description see, for example, Woods (220, page 356)) to determine the state of polarization of liquids. This method is particularly useful for the determination of ρ_h when ρ_v is small and has been employed by Balakrishnan (8). It has been the reviewer's experience, however, that the direct measurement of the polarization components can successfully be made with two polaroids or nicols acting as polarizer and analyzer and with a photomultiplier to determine the intensity.

There are two troublesome factors in depolarization measurements which reduce, somewhat, the usefulness of the method. These are the errors due to secondary or multiple scattering and those due to the convergence of the incident light beam. If light scattered from one particle is rescattered, this secondary scattering can result in large values of ρ_u and ρ_v and small values of ρ_h irrespective of the size, shape, or anisotropy of the particles. This problem has been investigated in detail by several workers, including Tichanowsky (205), Rousset (180), and Strauss (200). Tichanowsky (205) applied his theory to light scattering from the sky, which gives a depolarization apparently due to secondary scattering. According to Rousset (180), as a result of secondary scattering the value of ρ_h will depend on the shape of the illuminated volume of the scattering system and will be greater the closer the shape of the volume approaches a cube. The theory has been fully confirmed by Rousset (180) and by Mookerjee (127) in their depolarization studies of liquid mixtures at the critical mixing temperature. Mookerjee (127) has criticized Krishnan for his failure to take secondary scattering into account in his studies of liquids and liquid mixtures (Krishnan (97)). The problem of scattering from liquids and solutions will be considered in detail later in this review. Krishnan has also been criticized by Parthasarathy (145) (see, however, Krishnan (102)) for not correcting his depolarization values for convergence. Because of the finite size of the light source it is impossible to achieve perfectly parallel light in the incident beam. According to Gans (67), the convergence of the incident beam increases ρ_u and ρ_v by a term which is proportional to the square of the angle of convergence. ρ_h is decreased by a term proportional to the square of the convergence angle and inversely proportional to ρ_v, and therefore when there is convergence ρ_h is less than unity although the scattering particles may be of small size. According to Rao (169) (see Bhagavantum (13, Chapter 4)), no convergence correction is necessary if the scattered light comes from a point at the focus of the converging incident beam. In the theory of Strauss (200) the depolarization, ρ_u, for a dilute solution of spheres increases approximately linearly with the turbidity of the sample. The constant of proportionality increases as the size of the incident beam is increased. These results are in agreement with those obtained by Lonti (118). In figure 10 are shown Lonti's depolarization measurements at two different wave lengths for solutions of the hemocyanin of *Helix pomatia*. The turbidity and therefore the depolarization is greater for the shorter wave length. The depolarization, as does the turbidity, increases with increasing concentration (figure 10A). Figure 10B shows that the depolarization increases nearly linearly with the diameter of the incident beam. For this system, at least, in order to obtain the true depolarization it is necessary to extrapolate to infinite dilution and to small beam diameter. An indication of secondary scattering is usually given when the depolarization of a system is strongly dependent on concentration and wave length. For less turbid systems than that studied by Lonti, secondary scattering may be less important. The necessity of working with extremely dilute solutions in making depolarization measurements of colloidal solutions is clearly shown in the work of Hoover, Putnam, and Wittenberg (88) with bentonite and ferric oxide sols (see also Singh (189)).

In nearly all cases of high-polymeric molecules in solution ρ_v is found to be small (natural rubber, Gehman and Field (70); synthetic rubbers, Tsvetkoff and Frisman (207); cellulose acetate, polyvinyl chloride, and polystyrene, Doty and Kaufman (44); myosin, Lotmar (120); and tobacco mosaic virus, Doty (42) and Oster (141)). This indicates that the molecules are nearly isotropic in solution. It is difficult to evaluate results obtained for ρ_h, since in most cases not enough measurements were taken in the low concentration range to allow

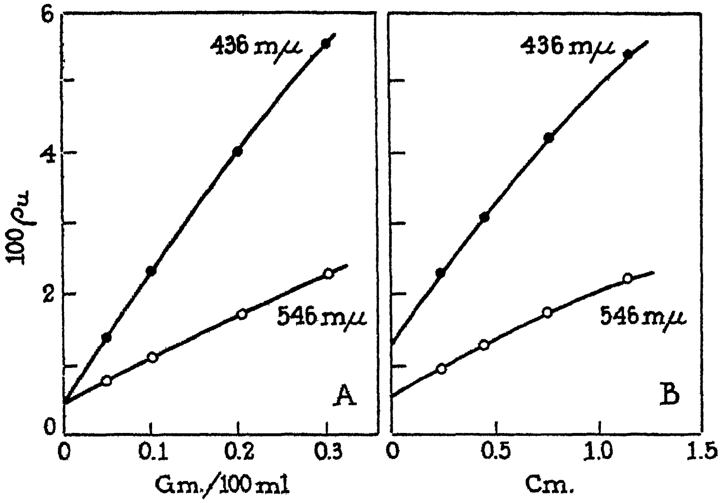


FIG. 10. Depolarization of light scattered at 90° from solutions of hemocyanin (*Helix pomatia*): (A) depolarization as a function of protein concentration; (B) depolarization as a function of incident beam diameter (Lonti (118)).

an extrapolation to infinite dilution (see, however, Gehman and Field (70), Lotmar (120), Doty (42), and Oster (141)). In his studies of ionic solutions, Hogrebe (87) found that the depolarization ρ_u (and therefore ρ_v, since $\rho_h \simeq 1$) when extrapolated to infinite dilution was considerable for unsymmetrical ions. Even symmetrical ions showed a slight depolarization, which Hogrebe attributes to the formation of anisotropic scattering units due to the interaction of the ions and the surrounding water molecules.

The depolarization of scattered light from large colloidal particles oriented by flowing in a tube has been examined by Diesselhorst and Freundlich (39). By making observations of the scattered polarized light perpendicular to and in the direction of flow, they were able to distinguish between spherical, disc-shaped, and rod-shaped colloidal particles (see Freundlich (57, Volume 2, page 81)). In some ways this resembles the method of flow birefringence (for review, see Edsall (47)). Depolarization studies have also been made on colloidal particles which are oriented with an electric or magnetic field (see, for example, Krishnan (101), Errera, Overbeck, and Sack (51), Mueller (132), Lauffer (113), and Subrahmanya, Doss, and Rao (203)). The theory and experimental results of the electroöptical properties of colloids have been discussed in detail by Heller (83) and by Mueller and Sackmann (133).

III. NON-INDEPENDENT PARTICLES

In the treatment for independent particles given above the particles were considered to be in random positions with respect to one another. For liquids and non-ideal solutions, however, the thermal movements of the constituent members of the scattering system are not independent, and it cannot be expected that the total intensity of scattered light will be the mere summation of the intensities from the individual particles. Some destructive interference will occur and result in a decrease in intensity of scattered light from that expected for the same weight of independent particles. In principle, the phase relationships between the wavelets scattered by the various elements of a condensed system can be computed; however, the mathematical difficulties are circumvented by considering the problem as one in fluctuations. The elementary ideas of the theory of fluctuations have been given by Landau and Lifshitz (109, Chapter 6), Tolman (206, Section 114), and Slater (191, Chapter 7). More complete treatments are given by Fürth (58) and especially by Leontovich (115, Chapter 3). It was clearly shown by Gibbs (71; see especially Chapters 7, 8, and 15) that thermodynamic quantities which are usually measured represent time averages over a large number of molecules. If, however, we consider a small volume in a system, the thermodynamic state of the system described by some thermodynamic quantity x may differ at any instant from the average value $\bar{x}$. The time average of this deviation, $x - \bar{x}$, may be zero, but if the volume is chosen small enough so as to include only a small number of molecules, the time average of the square of the deviations, or fluctuation, may differ considerably from zero. Also, according to Gibbs, the average value of any quantity in a small volume is the same whether the averaging is taken over a long period of time in the one volume element or whether the instantaneous value for a great number of such volume elements is averaged.

Smoluchowski (192) used the concept of thermodynamic fluctuations to explain the great intensity of scattering observed for liquids near their critical temperatures. According to Smoluchowski, the molecules in a liquid are not distributed uniformly, but rather in any small volume of the liquid the number of particles varies from instant to instant as a consequence of their thermal motions. This local fluctuation in density of particles will give local inhomogeneities in the index of refraction and will scatter light. In the case of liquids, the fluctuations in density are increased as the compressibility is increased and at the critical temperature the light scattering should theoretically be infinite. Smoluchowski's theory was further extended by Einstein (48) for liquid mixtures to include inhomogeneities in the refractive index due to fluctuations in concentration.

The elementary principles of the theory of fluctuations will now be briefly reviewed, since much of the light-scattering phenomena to be discussed can be explained in terms of this theory.

In order to bring about a change in a given system of some thermodynamic quantity from its average value $\bar{x}$ to some value x, a certain amount of free energy must be expended. The probability of such a change is proportional to

$$e^{-\Delta A/kT} \tag{33}$$

where A is the Helmholtz free energy and $\Delta A = A(x) - A(\bar{x})$. k is Boltzmann's constant, and T is the absolute temperature. Boltzmann's definition of entropy is a special case of equation 33 in which the energy and volume are kept constant. The temperature is assumed constant throughout the fluctuation process. According to equation 33, the probability of a deviation in x decreases rapidly the greater the deviation. If only small deviations about the average value are considered, the free energy difference ΔA may be expanded in a Taylor series in the deviation $\Delta x = x - \bar{x}$, or

$$\Delta A = \left(\frac{\partial A}{\partial x}\right)_{x=\bar{x}} \Delta x + \frac{1}{2!}\left(\frac{\partial^2 A}{\partial x^2}\right)_{x=\bar{x}} (\Delta x)^2 + \frac{1}{3!}\left(\frac{\partial^3 A}{\partial x^3}\right)_{x=\bar{x}} (\Delta x)^3 + \cdots \tag{34}$$

But $\left(\frac{\partial A}{\partial x}\right)_{x=\bar{x}}$ is zero, since the free energy of a closed system of constant temperature is a minimum at equilibrium. For small deviations, terms higher than the squared term are small, so the free energy difference is given by

$$\Delta A \simeq \frac{1}{2}\left(\frac{\partial^2 A}{\partial x^2}\right)_{x=\bar{x}} (\Delta x)^2 \tag{35}$$

Insertion of this value into equation 33 gives a Gaussian distribution whose second moment or average value (averaged over Δx) of the square of the deviation is

$$\overline{(\Delta x)^2} = \frac{kT}{\left(\frac{\partial^2 A}{\partial x^2}\right)_{x=\bar{x}}} \tag{36}$$

It can further be shown that the average value of the product of deviations of independent quantities is zero, that is:

$$\overline{\Delta x_i \Delta x_j} = 0 \tag{37}$$

1. Pure liquids

Following Smoluchowski (192) (see also Einstein (48)) we shall consider light scattered from an element of volume δV of the liquid which is small compared with the wave length of the incident light, yet which is sufficiently large to include a great number of molecules (the exact dimensions of the volume element are unimportant for the discussion). The fluctuation in the number of particles in the volume element will result in a fluctuation in the optical dielectric constant. Any particular volume element may be likened to a small particle with optical dielectric constant different from that of the surrounding homogeneous medium in which it is immersed. From equation 4 it is seen that the effective square of the polarizability for the volume δV is given by

$$\frac{(\delta V)^2}{16\pi^2 \epsilon_0^2} \overline{(\Delta\epsilon)^2} \tag{38}$$

The inhomogeneities in density of particles are randomly distributed throughout the total volume of the liquid, so that the total intensity of scattering is the sum of the contributions from each of the volume elements. The intensity per unit volume of scattering material is then obtained by inserting the expression for the square of the polarizability, equation 38, into equation 1 and dividing by the sum of the volume elements, or

$$\frac{i}{I_0} = \frac{\pi^2}{2\lambda^4 r^2} \overline{(\Delta\epsilon)^2} \delta V(1 + \cos^2\theta) \tag{39}$$

and the turbidity is

$$\tau = \frac{8\pi^3}{3\lambda^4} \overline{(\Delta\epsilon)^2} \delta V \tag{40}$$

The optical dielectric constant ϵ is a function of the density σ and the temperature, i.e.

$$\Delta\epsilon = \left(\frac{\partial\epsilon}{\partial\sigma}\right)_T \Delta\sigma + \left(\frac{\partial\epsilon}{\partial T}\right)_\sigma \Delta T \tag{41}$$

For liquids $\left(\frac{\partial\epsilon}{\partial T}\right)_\sigma$ is about 10^{-5} (Levin (117)) and therefore the second term on the right of equation 41 is negligible compared with the first term, since $\left(\frac{\partial\epsilon}{\partial\sigma}\right)_T$ is of the order of unity. The fluctuation in the optical dielectric constant is then given by

$$\overline{(\Delta\epsilon)^2} = \left(\frac{\partial\epsilon}{\partial\sigma}\right)_T^2 \overline{(\Delta\sigma)^2} \tag{42}$$

With the use of well-known thermodynamic relations the fluctuation in density for the volume element δV may be shown from equation 36 ($x = \sigma$) to be

$$\overline{(\Delta\sigma)^2} = \frac{kT\beta\sigma^2}{\delta V} \tag{43}$$

where β is the isothermal compressibility. From equation 39 the intensity per unit volume and the turbidity are given by

$$\frac{i}{I_0} = \frac{\pi^2}{2\lambda^4 r^2} \left(\sigma \frac{\partial\epsilon}{\partial\sigma}\right)_T^2 kT\beta(1 + \cos^2\theta) \tag{44}$$

and by

$$\tau = \frac{8\pi^3}{3\lambda^4} \left(\sigma \frac{\partial\epsilon}{\partial\sigma}\right)_T^2 kT\beta \tag{45}$$

It is necessary to relate the optical dielectric constant to the density in order to give a value for $\sigma(\partial\epsilon/\partial\sigma)$ in terms of conveniently observable quantities. The optical dielectric constant of a liquid is conventionally related to the density by the Clausius–Mossotti equation. This equation is derived by considering the electric field in a small region of the liquid as that given by the Lorentz local field (Lorentz (119, page 303)), which is a mathematical device and is subject to criticism on physical grounds (for a critique of Lorentz's theory, see Van Vleck (212)). A more physically plausible treatment of the local field is given by Onsager (135), according to whom the field in a small region of the liquid is that given by the field in a real cavity imbedded in a medium of homogeneous dielectric constant. According to Onsager

$$\frac{(\epsilon - 1)(2\epsilon + 1)}{9\epsilon} = K\sigma \tag{46}$$

where K is a constant for a given liquid. The reviewer has found (unpublished calculations) that equation 46 holds better for liquids and liquid mixtures than does the Clausius–Mossitti equation (for recent data on the variation of index of refraction of liquids and liquid mixtures with density, see Rosen (179)). Equation 46 gives:

$$\sigma\frac{\partial\epsilon}{\partial\sigma} = (\epsilon - 1)\left(\frac{2\epsilon^2 + \epsilon}{2\epsilon^2 + 1}\right) \tag{47}$$

Since ϵ is usually less than 2 for most liquids, the second factor in parentheses on the right may, to a close approximation, be taken as unity. The intensity per unit volume and the turbidity then become

$$\frac{i}{I_0} = \frac{\pi^2}{2\lambda^4 r^2}(\epsilon - 1)^2 kT\beta(1 + \cos^2\theta) \tag{48}$$

$$\tau = \frac{8\pi^3}{3\lambda^4}(\epsilon - 1)^2 kT\beta \tag{49}$$

A similar result was obtained by Ramanathan (167), using a different and somewhat questionable physical argument.

Equations 48 and 49 must be further modified to correct for the depolarization of the scattered light. According to Ramanathan (166, 167) equations 48 and 49 must be multiplied by the Cabannes factors equations 14 and 15, respectively, to account for the fluctuations in orientation. The depolarization ρ_u used is that observed for the liquid.

The early work of Keesom (93) on ethylene and the later work of Ramanathan (166), Venkateswaran (214), Martin and Lehrman (123), Krishnan (96), Raman and Ramanathan (161), Cabannes (25, part 1), Peyrot (147), and Rao (170) on several other liquids shows general agreement with equation 48. Rao (170) has studied a few liquids over a wide range of temperatures. He found that equation 48 with its appropriate depolarization factor held very closely up to temperatures a few degrees below the critical temperature. Use of the Clausius–

Mossotti equation relating the optical dielectric constant and the density gave, however, values of the intensity which were greater than those observed.

In general, the depolarization for liquids is five or more times greater than that exhibited by the molecules in the gaseous state. The depolarization for normal alcohols increases with increasing length and greater anisotropy of the carbon chain, but for fatty acids there are alternations in the depolarization with increasing carbon chain length which resemble the marked alternation in melting points and dissociation constants exhibited by these compounds. More recent data on the depolarization by liquids have been compiled by Cabannes and Rousset (26) (see Peyrot (148), who also discusses error of measurement). The larger values of the depolarization of the molecules in the liquid state are attributed by Raman and Krishnan (159, 160) to the polarizability induced by the surrounding medium. If the inner field is treated as homogeneous and of the Lorentz type, the calculated depolarization for liquids is too high. Raman and Krishnan (159, 160) therefore treat the molecules and their immediate surrounding fluid as polarizable ellipsoids and calculate depolarizations for some long-chain hydrocarbons which are in fair agreement with observed values. They also apply these concepts to the Kerr effect for non-polar liquids. Mueller (131) has criticized the treatment of Raman and Krishnan for its failure to consider the possibility of hindered rotation between molecules in the condensed state. The theory of Mueller has, however, certain drawbacks, since it is based on the Lorentz inner field and on the cybotactic theory of liquids. According to the cybotactic theory due to Stewart (197) there are, at any instant in the liquid, groups of as many as a hundred molecules which are in a relatively ordered array and which are rapidly exchanging members with the continuous region between them. Although it is possible that for liquids consisting of long-chain molecules (and particularly those investigated by Stewart which contain OH and COOH groups) there exist such groups (see Frenkel (56, Chapter 5, Section 10) for the conditions of stability of cybotactic groups), more recent x-ray data of ordinary liquids (Warren (218), Ginrich (72)) indicate that in most liquids only local order exists and extends over mainly the first shell of nearest neighbors (for a critical discussion see Prins (153), and especially Bernal (11)). In view of the criticisms discussed earlier by Mookerjee (127) and by Parthasarathy (145) of the depolarization results of R. S. Krishnan, it cannot be claimed at the present time that the depolarization studies prove the existence of cybotactic groups. In the case of liquid crystals, however, Chatelain (28) (see also Zwetkov (227)) in his light-scattering studies has shown the presence of molecular groupings comparable in size to the wave length of the incident light. The theory of dielectrics of Onsager (135) has been extended by Kirkwood (95) to include the case of hindered rotation of the molecules, so that the means are at hand to develop a complete theory of depolarization of non-polar and polar liquids. The theory would also be suitable to explain the Kerr effect for these liquids. In the case of highly elongated molecules it would be necessary to modify the Onsager local field.

2. Non-ideal solutions

The extension by Einstein (48) of Smoluchowski's theory (192) to include liquid mixtures is suitable for any solution as long as the particles are small compared to the wave length of the incident light. If they are not, a correction factor for the dissymmetry of the scattering must be applied. According to Einstein (48) fluctuations in the concentration in an element of volume δV will be large; and since, in general, the optical dielectric constants of the solute and the solvent differ, the resultant fluctuation in the optical dielectric constant will cause light to be scattered. The fluctuation in concentration may be determined from equation 36 (see Gibbs (71, Chapter 15)). The fluctuation in dielectric constant is related to the fluctuation in concentration of the solute (for convenience the concentration of the solute c is given in grams per milliliter of solution) by

$$\overline{(\Delta\epsilon)^2} = \left(\frac{\partial\epsilon}{\partial c}\right)^2 \overline{(\Delta c)^2} \tag{50}$$

where

$$\overline{(\Delta c)^2} = \frac{kT}{\left(\dfrac{\partial^2 A}{\partial c^2}\right)_{\bar{c},V}}$$

Now

$$\left(\frac{\partial A}{\partial c}\right)_{\bar{c},V} = \mu_0 \frac{\partial \nu_0}{\partial c} \tag{51}$$

where μ_0 is the Gibbs chemical potential of the solvent and ν_0 is the number of solvent molecules per milliliter of solution. For the volume element δV, the variation in number of solvent molecules with the variation in the concentration of the solute is given closely by

$$\frac{\partial \nu_0}{\partial c} = -\frac{N\delta V}{\bar{V}_0\,\bar{c}} \tag{52}$$

where N is Avogadro's number and $\bar{V}_0$ is the partial molal volume of the solvent. Insertion of equation 50 with equations 51 and 52 into equation 40 gives for the turbidity (at this point the average solute concentration will be written as c)

$$\tau = \frac{8\pi^3}{3\lambda^4} \frac{RT\bar{V}_0 c}{N\left(-\dfrac{\partial\mu_0}{\partial c}\right)} \left(\frac{\partial\epsilon}{\partial c}\right)^2 \tag{53}$$

where R is the gas constant. If the system exhibits depolarization, equation 53 must be multiplied by the Cabannes factor (equation 15).

Equation 53 gives the light scattering in terms of the thermodynamic properties of the solvent. The osmotic pressure P of a solution is related to the chemical potential of the solvent by $P\bar{V}_0 = -N\mu_0$ and gives for equation 53:

$$\tau = \frac{8\pi^3}{3\lambda^4} \frac{RTc}{N\left(\dfrac{\partial P}{\partial c}\right)} \left(\frac{\partial\epsilon}{\partial c}\right)^2 \tag{54}$$

Equation 54 is in the form given by Raman and Ramanathan (161) and by Debye (33, 34). For dilute solutions, the osmotic pressure may be written in terms of the molecular weight M of the solute and of the solute concentration by

$$P = \frac{c}{M} RT + Bc^2 \tag{55}$$

where B is a measure of the deviation from ideality. In the limit of $c \rightarrow 0$ we obtain for ideal solutions, after the contribution of the scattering of the solvent has been subtracted (the contribution from density fluctuations of the solute is negligible),

$$H\left(\frac{c}{\tau}\right)_{c=0} = \frac{1}{M} \quad \text{where} \quad H = \frac{8\pi^3}{3N\lambda^4}\left(\frac{\partial\epsilon}{\partial c}\right)^2 \tag{56}$$

which is identical with equation 10. For dilute solutions the turbidity may be written in the form

$$H\frac{c}{\tau} = \frac{1}{M} + \frac{2Bc}{RT} \tag{57}$$

A plot of $H(c/\tau)$ *versus* c gives a straight line whose intercept is the reciprocal of the molecular weight of the solvent and whose slope is determined by B. Doty, Zimm, and Mark (46) have determined the molecular weights of fractions of polystyrene and cellulose acetate by this method and obtain results which are in agreement with direct osmotic-pressure measurements of these samples. Similar studies have been made by P. P. Debye (37) of polymers which had been subject to milling. In their work on cellulose acetate, Stein and Doty (194) corrected the molecular weights obtained by extrapolation with the dissymmetry factor. A similar procedure was adopted by Oster, Doty, and Zimm (142), who obtained a molecular weight for tobacco mosaic virus in agreement with that obtained by other methods.

As shown by Zimm and Doty (224), the molecular weight obtained by the light-scattering method is the weight-average molecular weight, because, as may be seen directly from Rayleigh's equation, the intensity of scattering is proportional to the number of scatterers and to the square of their volumes or molecular weights. According to Zimm and Doty (224) the curvature of the $H(c/\tau)$ *versus* c curve is determined by the higher moments of the molecular weights of the sample. In principle, the spread of the molecular weight distribution could be determined from the curvature. In practice, however, this is not feasible because of the relatively poor ability of the light-scattering method to resolve different sizes (Waser, Badger, and Schomaker (219)). The slope of the linear portion of the curve determines the value of B, which can be related to the size and shape of the solute molecules and to their interactions with each other and with the solvent. In general, the greater the solubility and the more the particles deviate from spherical shape, the greater the slope. If the molecular weight of the polymer is the same in different solvents, the curves should converge at zero concentration of the polymer. Ewart, Roe, Debye, and McCartney (52) have benzene and methanol (see figure 11). These workers attribute the lack of convergence at infinite dilution to selective absorption of benzene by the polystyrene and not to any changes in the molecular weight of polystyrene in the various solvent mixtures. The alcohol serves as a precipitant, and the turbidity is increased considerably by its presence in small quantities well below the concentration necessary for two-phase separation. Ewart, Roe, Debye, and McCartney have shown that the magnitude of the selective absorption can be determined by turbidity measurements. In the case of a solvent–precipitant pair, such as butanone and 2-propanol, which have nearly equal refractive indices, or in the case of a pure liquid solvent or a solvent mixture in which no selective absorption by the solute occurs, the $H(c/\tau)$ *versus* c curves converge at infinite dilution. For further discussion of applications to high-polymeric systems see the recent review by Mark (121a).

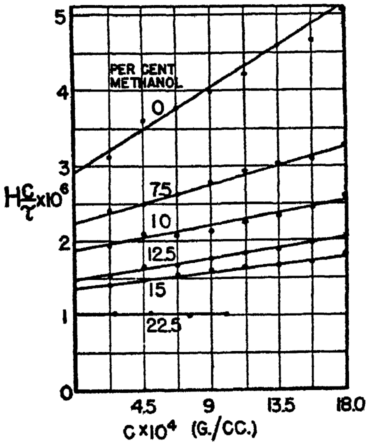


FIG. 11. Reciprocal specific turbidity as a function of concentration of polystyrene in benzene–methanol mixtures (Debye (34); Ewart, Roe, Debye, and McCartney (52)).

3. Liquids at the critical temperature

When a liquid is brought to its critical temperature or when a liquid mixture is brought to its critical temperature of mixing, it assumes a milky opalescence on illumination with white light. The theories of Smoluchowski (192) and of Einstein (48) properly explain the large scattering exhibited by such systems near the critical temperature but predict too high an intensity of scattering for systems very close to or at the critical temperature. Furthermore, several authors have found that in addition to there being less scattering than is to be expected from equation 48, the scattering is proportional to $1/\lambda^2$ rather than to $1/\lambda^4$ (Zernicke (221), Andant (2), and Bhattacharya (14)). Ornstein and Zernicke (136) attribute the discrepancy with the Smoluchowski–Einstein theory to failure to consider the influence of deviations of density or concentration in one volume element on those in another volume element. According to Ornstein and Zernicke (137) the mean value of the product of the deviations in one volume element and those in another is not zero as in equation 37, but is proportional to the radial distribution of the molecules about any one molecule (compare Zimm (222)). In place of equation 48, Ornstein and Zernicke obtain for the intensity of scattering per unit volume

$$\frac{i}{I_0} = \frac{\pi^2(\epsilon - 1)^2}{2\lambda^4 r^2} \frac{kT(1 + \cos^2 \theta)}{\frac{1}{\beta} + \left(\frac{2\pi g}{\lambda} \sin \frac{\theta}{2}\right)^2} \tag{58}$$

where g is a measure of the size of the sphere of influence of the intermolecular forces. At temperatures below the critical temperature the second term in the denominator is negligible compared to $1/\beta$ and equation 58 reduces to equation 48. Very close to or at the critical temperature, however, the compressibility, β, is very great, and the second term in the denominator predominates; and therefore the intensity becomes proportional to $1/\lambda^2$. The quantity g can be obtained from experiment and has been given in terms of the radial distribution function by Ornstein and Zernicke (137). Some objections to the more explicit definition of g have been raised by Placzek (150) and by Rocard (178); however, equation 58 reproduces the general features of the scattering at the critical temperature. Mueller (131) has extended the theory to take into account non-independent fluctuations in the orientation of anisotropic molecules.

Rousset (180) has examined several liquid mixtures at the critical mixing temperature. He has observed the dissymmetry in scattering which is predicted by equation 58 when the second term in the denominator predominates.

The light-scattering method is also useful for studying phase changes besides those which occur at the critical temperature. It could be used, for example, to detect possible premelting at temperatures just below the melting point of a solid (Ubbelohde (209); for theory, see Frenkel (56, chapter 7, Section 3)) and to determine the kinetics of phase changes. The light-scattering method has been used by Donnan and Krishnamurti (40) to study sol–gel transformations. They found that for agar solutions the intensity and depolarization of scattered light increase markedly when the sol is transformed into a gel on cooling. These authors attribute this change in scattering to the formation of micelles in the gel. Tobacco mosaic virus gels, however, show less scattering than that of the sols because the gel is an ordered structure (Bernal and Fankuchen (12), Oster (141)).

4. Interfaces

It was early recognized by Smoluchowski (192) that there should be increased scattering by the surface of a liquid as the critical temperature is approached, because of the increased density fluctuations. Mandelstam (121) soon after developed a theory of the scattering of surfaces which is the two-dimensional analog of the volume scattering of Ornstein and Zernicke (136, 137). According to Mandelstam, at temperatures below the critical temperature the intensity of scattering from a surface, i_s, per unit area of surface is given by

$$\frac{i_s}{I_0} = \frac{4kT(\epsilon - 1)^2}{\gamma\lambda^2 r^2} f \tag{59}$$

where f is a function of the angles of incidence and of observation and depends on the degree of polarization of the incident beam and γ is the interfacial tension. As the surface tension is decreased, the density fluctuations at the surface increase and the intensity of scattering increases. The theory has been extended by Gans (64) to include liquid metal surfaces and the general theory has been modified slightly by Gans (66) and by Andronov and Leontovich (4). Detailed investigations by Raman and Ramdas on the intensity of light scattered from surfaces of metallic liquids (162), of transparent liquids (163), and of liquid carbon dioxide near the critical temperature (164) show good agreement with Mandelstam's theory. The scattered light which is usually observed close to the beam reflected from the surface does not, however, show exact agreement in angular distribution predicted by the theory (Ramdas (168); see also Jagannathan (89) and Hariharan (82)).

Raman and Ramdas (164) found that the intensity of scattering increased when surface-active agents were applied to water. The light-scattering method affords a convenient method for studying surface films especially as regards their continuity (see Zocher and Stiebel (226) and Adams (1)) and could also be used to study the orientation of molecules at surfaces. Schaeffer (183) has studied the light-scattering properties of monolayers on metallic surfaces. Since in equation 59 γ refers to the interfacial tension, the light-scattering method provides a simple way to determine the interfacial tension.

5. Fine structure of the Rayleigh line

Fine structure was first observed by Gross (75) in an examination, under high resolution, of light scattered at 90° by liquids. In general, one observes with a spectroscope or interferometer that the scattered light consists of three lines: an undisplaced center line and two lines on either side with wave lengths slightly different from that of the incident light. Usually these lines can be distinguished from the Raman scattering of the liquid. The displaced lines can be attributed to the Doppler shift of the scattered radiation which is reflected from the system of Debye sound waves excited by thermal energy (Brillouin (22), Leontovich and Mandelstam (116); see also Frenkel (56, Chapter 4, Section 8)).[7] According to Landau and Placzek (110), the undisplaced line, which in general is brighter, is due to entropy fluctuations which vary relatively slowly with time. The ratio of the intensity of the center undisplaced line, I_c, to the intensities of the displaced doublets, $2I_d$, is given by Landau and Placzek (110) as

$$\frac{I_c}{2I_d} = \frac{C_p - C_v}{C_v} \tag{60}$$

where C_p and C_v are the specific heats at constant pressure and volume, respectively. A complete derivation of this formula is given by Gross (78). The ratio of the intensities of the central line to that of the doublets is given by the ratio of the contributions to the fluctuations in the optical dielectric constant due to fluctuations in entropy and those due to fluctuations in pressure associated with ordinary sound waves, or

---

[7] *Added in proof:* A. B. Bhatia and K. S. Krishnan (Proc. Roy. Soc. (London) **A192**, 181 (1948)) have shown that the intensity of the displaced lines is given by the same expression derived by I. Waller (Uppsala Univ. Årssk. (1925)) for x-ray scattering from substances when thermal vibrations are taken into account.

$$\frac{I_c}{2I_d} = \frac{\left(\frac{\partial v}{\partial s}\right)_p^2 \overline{(\Delta S)^2}}{\left(\frac{\partial v}{\partial p}\right)_s^2 \overline{(\Delta p)^2}} \tag{61}$$

With the aid of equation 36 and some well-known thermodynamic relations, equation 61 leads to the Landau and Placzek formula, equation 60. Gross (76) and Birus (15) (see also Meyer and Ramm (123a) and Ramm (168a)) found that this formula held for a few liquids. For some substances, for example water and quartz, $C_p \simeq C_v$, so the center line is very feeble. However, for a number of other liquids, e.g., benzene, the center line has a greater intensity than that given by the Landau and Placzek formula (Gross (76), Venkateswaren (213)). The very intense center line can, in several cases, be attributed to orientation fluctuations by anisotropic molecules and is highly depolarized (Gross (77), Venkateswaran (213)). The intensity of the center line is increased with increasing viscosity, that is, with increasing rotational relaxation time of the anisotropic molecules (see Leontovich (114)). However, it has been found by Gross and Siromyatnikov (81) and by Bai (6) that for very viscous liquids which do not contain anisotropic molecules, the center line is of greater intensity than that predicted by the Landau and Placzek formula and is not depolarized. This result is as yet not completely explained, but even in the absence of a complete theory it is clear that the ratio of intensities of the center line to that of the doublets is a measure of the amount of thermal energy apportioned between the pressure and the entropy fluctuations. A study of the Rayleigh scattering lines for certain solids gives some information about molecular rotation in solids (Gross and Raskin (79)).

According to Ginsburg (74), the widths of the lines must be considered when their intensities are determined. He has related the width of the central line to the heat conductivity and the width of the doublets to the absorption of sound in the liquid. Recent work by Gross and Raskin (79), by Fabelinsky (53), and by Vuks (217) on the detailed structure of the Rayleigh lines indicates confirmation of Ginsburg's theory.

In view of the extraordinary physical properties of helium II, especially its ability to propagate two types of sound waves, it might be expected that this substance would show unusual fine structure of the Rayleigh scattering (for discussion, see Ginsburg (73) and Argawala and Chowdri (5)), but no experimental results on the fine structure have as yet been reported. Jakovlev (90) has found that the intensity of scattering by helium II below 2° A. is that given by equation 48. As Ginsburg (73) has pointed out, the observed intensity is that expected from Landau's theory of helium II and is less by a factor of ten thousand than that for a condensed Bose–Einstein gas calculated by Fusov, Belinsky, and

Galanin (59) (see also Singh (188), Schiff (184), and Galanin (60)). Incidentally, Fusov, Belinsky, and Galanin (59) have also calculated the light scattering from a Fermi–Dirac gas and derive results which explain the incoherent part of the scattering of x-rays by metals (see also the interesting treatment by Frenkel (54, Chapter 6, Section 35) of electrical conductivity as a problem in fluctuation scattering). In their theoretical treatment of the fluctuations they use the Bose–Einstein and Fermi–Dirac distributions instead of the Maxwell–Boltzmann distribution given by equation 33.

IV. REFERENCES

(1) ADAM, N. K.: Trans. Faraday Soc. **29**, 90 (1933).
(2) ANDANT, A.: Compt. rend. **176**, 430 (1923); Ann. phys. **1**, 346 (1924).
(3) ANDREASON, A. H. M.: Tek. Tid. **76** (1946).
(4) ANDRONOV, A., AND LEONOTOVICH, M.: Z. Physik **38**, 485 (1926).
(5) ARGAWALA, B. K., AND CHOWDRI, A. G.: Nature **160**, 750 (1947).
(6) BAI, K. S.: Proc. Indian Acad. Sci. **A13**, 439 (1941); **A15**, 338, 349, 357 (1942).
(7) BAILEY, E. D.: Ind. Eng. Chem., Anal. Ed. **18**, 365 (1946).
(8) BALAKRISHMAN, T. A. S.: Proc. Indian Acad. Sci. **A14**, 235 (1941).
(9) BARDWELL, J., AND SIVERTZ, C.: Can. J. Research **B25**, 255 (1947).
(10) BARNETT, C. E.: J. Phys. Chem. **46**, 69 (1942).
(11) BERNAL, J. D.: Trans. Faraday Soc. **33**, 27 (1937).
(12) BERNAL, J. D., AND FANKUCHEN, I.: J. Gen. Physiol. **25**, 11 (1941).
(13) BHAGAVANTUM, S.: *Scattering of Light and the Raman Effect.* Chemical Publishing Co., Inc., Brooklyn, New York (1942).
(14) BHATTACHARYA, D. K.: Proc. Indian Assoc. Cultivation Sci. **8**, 277 (1923).
(15) BIRUS, K.: Physik. Z. **39**, 80 (1938).
(16) BISCOE, J., AND WARREN, B. E.: J. Applied Phys. **13**, 364 (1942).
(17) BLUMER, H.: Z. Physik **32**, 119 (1925); **38**, 304 (1926).
(18) BORN, M.: Ann. Physik **55**, 177 (1918).
(19) BORN, M.: *Optik.* J. Springer, Berlin (1933).
(20) BOUTARIC, A., AND BRETON, J.: J. chim. phys. **36**, 193 (1936).
(21) BRESLER, S., AND FRENKEL, J.: Acta Physicochim. U.R.S.S. **11**, 487 (1939).
(22) BRILLOUIN, L.: Ann. phys. **17**, 88 (1922).
(23) CABANNES, J.: Compt. rend. **160**, 62 (1915).
(24) CABANNES, J.: Ann. phys. **15**, 5 (1921).
(25) CABANNES, J., AND ROCARD, Y.: *La diffusion moléculaire de la lumière.* Les Presses Universtaires de France, Paris (1929).
(26) CABANNES, J., AND ROUSSET, A.: *Tables annueles de constantes et donneés numériques,* Vol. 16. Hermann et Cie, Paris (1937).
(27) CASPERSSON, T.: Kolloid-Z. **60**, 151 (1932); **65**, 162 (1933).
(28) CHATELAIN, P.: Compt. rend. **218**, 652 (1944); **222**, 229 (1946).
(29) CLEWELL, D. H.: J. Optical Soc. Am. **31**, 521 (1941).
(30) COMPTON, A. H., AND ALLISON, S. K.: *X-Rays in Theory and Experiment.* D. Van Nostrand Co., Inc., New York (1935).
(31) DEBYE, P.: Ann. Physik **30**, 59 (1909).
(32) DEBYE, P.: Lecture given at the Polytechnic Institute of Brooklyn, Brooklyn, New York, November 25, 1944.
(33) DEBYE, P.: J. Applied Phys. **15**, 338 (1944).
(34) DEBYE, P.: J. Phys. Colloid Chem. **51**, 18 (1947).
(35) DEBYE, P., AND MENKE, H.: Forts. Röntgenforschung **2**, 1 (1931).
(36) DEBYE, P. P.: Thesis, Cornell University, 1944.

(37) Debye, P. P.: J. Applied Phys. **17,** 392 (1946).

(38) de Vore, J. R., and Pfund, A. H.: J. Optical Soc. Am. **37,** 826 (1947).

(39) Diesselhorst, H., and Freundlich, H.: Physik. Z. **17,** 117 (1916).

(40) Donnan, F. G., and Krishnamurti, K.: Colloid Symposium Monograph **7,** 1 (1930).

(41) Doty, P. M.: J. Polymer Sci., in press.

(42) Doty, P. M.: Personal communication.

(43) Doty, P. M., Affens, W. A., and Zimm, B. H.: Trans. Faraday Soc. **42B,** 66 (1946).

(44) Doty, P., and Kaufman, H. S.: J. Phys. Chem. **49,** 453 (1945).

(45) Doty, P., Wagner, H., and Singer, S.: J. Phys. Colloid Chem. **51,** 1 (1947).

(46) Doty, P. M., Zimm, B. H., and Mark, H.: J. Chem. Phys. **14,** 43 (1946).

(47) Edsall, J. T.: In *Advances in Colloid Science,* Vol. 1. Interscience Publishers, Inc., New York (1942).

(48) Einstein, A.: Ann. Physik **33,** 1275 (1910).

(49) Engelhard, H., and Freiss, H.: Kolloid-Z. **81,** 129 (1937).

(50) Epstein, P. S.: Encykl. Math. Wiss. **5,** Part 3, p. 513.

(51) Errera, J., Overbeck, W., and Sack, H.: J. chim. phys. **32,** 681 (1935).

(52) Ewart, R. H., Roe, C. P., Debye, P., and McCartney, J. R.: J. Chem. Phys. **14,** 687 (1946).

(53) Fabelinsky, I. L.: Bull. acad. sci. U.R.S.S. (Sér. phys.) **9,** 186 (1945).

(54) Frenkel, J.: *Wave Mechanics.* Oxford University Press, London (1932).

(55) Frenkel, J.: Acta Physicochim. U.R.S.S. **19,** 51 (1944).

(56) Frenkel, J.: *Kinetic Theory of Liquids.* Oxford University Press, London (1946).

(57) Freundlich, H.: *Kapillarchemie,* 4th edition. Akademische Verlagsgesellschaft, Leipzig (1930).

(58) Fürth, R.: Chapter 6 in *Handbuch der Physik,* Vol. 4. J. Springer, Berlin (1929).

(59) Fusov, V., Belinski, S., and Galinin, A.: Ucheniye Zapiski, **No. 74,** 59 (1944).

(60) Galanin, A.: J. Exptl. Theoret. Phys. (U.R.S.S.) **10,** 1267 (1940).

(61) Gans, R.: Ann. Physik **37,** 881 (1912).

(62) Gans, R.: Ann. Physik **62,** 330 (1920).

(63) Gans, R.: Z. Physik **27,** 164 (1924).

(64) Gans, R.: Ann. Physik **74,** 231 (1924).

(65) Gans, R.: Ann. Physik **76,** 29 (1925).

(66) Gans, R.: Ann. Physik **79,** 204 (1926).

(67) Gans, R.: Physik. Z. **28,** 661 (1927).

(68) Gans, R.: *Handbuch der experimental Physik,* Vol. 19. Akademische Verlagsgesellschaft, Leipzig (1928).

(69) Gans, R.: Physik. Z. **37,** 19 (1936).

(70) Gehman, S. D., and Field, J. E.: Ind. Eng. Chem. **29,** 793 (1937).

(71) Gibbs, J. W.: *Elementary Principles in Statistical Mechanics.* Yale University Press, New Haven (1902).

(72) Ginrich, N. S.: Rev. Modern Phys. **15,** 90 (1943).

(73) Ginsburg, V. L.: J. Phys. (U.S.S.R.) **7,** 305 (1943).

(74) Ginsburg, V. L.: Compt. rend. acad. sci. U.R.S.S. **42,** 168 (1944); Bull. acad. sci. U.R.S.S. (Sér. phys.) **9,** 174 (1945).

(75) Gross, E.: Nature **126,** 201 (1930).

(76) Gross, E.: Nature **126,** 400 (1930).

(77) Gross, E.: Compt. rend. acad. sci. U.R.S.S. **28,** 786 (1940).

(78) Gross, E.: Acta Physicochim. U.R.S.S. **20,** 459 (1945).

(79) Gross, E., and Raskin, S.: Bull. acad. sci. U.R.S.S. (Sér. phys.) **9,** 184 (1945).

(80) Gross, E., and Raskin, A.: Acta Physicochim. U.R.S.S. **17,** 127 (1942).

(81) Gross, E., and Siromyatnikov, A.: Compt. rend. acad. sci. U.R.S.S. **28,** 786 (1940).

(82) Hariharan, P. S.: Proc. Indian Acad. Sci. **A16,** 290 (1942).

(83) Heller, W.: Rev. Modern Phys. **14,** 390 (1942).

(84) Heller, W.: Phys. Rev. **68,** 5 (1945).

(85) Heller, W., Klevens, H. B., and Oppenheimer, H.: J. Chem. Phys. **14**, 560 (1946).

(86) Heller, W., and Vassy, E.: J. Chem. Phys. **14**, 505 (1946).

(87) Hogrebe, K.: Physik. Z. **39**, 23 (1938).

(88) Hoover, C. R., Putnam, F. W., and Wittenberg, E. G.: J. Phys. Chem. **46**, 81 (1942).

(89) Jagannathan, S.: Proc. Indian Acad. Sci. **A1**, 115 (1934).

(90) Jakovlev, I. A.: J. Phys. (U.S.S.R.) **7**, 307 (1943).

(90a) Jeans, J.: *Electricity and Magnetism*, 5th edition. Cambridge University Press, London (1925).

(91) Jobst, G.: Ann. Physik **78**, 157 (1925).

(91a) Johnson, I., and La Mer, V. K.: J. Am. Chem. Soc. **69**, 1184 (1947).

(92) Keen, B. A., and Porter, A. W.: Proc. Roy. Soc. (London) **A89**, 370 (1913).

(93) Keesom, H.: Ann. Physik **35**, 591 (1911).

(94) Kerr, J.: Phil. Mag. **50**, 337 (1875).

(95) Kirkwood, J. G.: J. Chem. Phys. **7**, 911 (1939).

(96) Krishnan, K. S.: Phil. Mag. **50**, 697 (1925).

(97) Krishnan, R. S.: Proc. Indian Acad. Sci. **A1**, 211 (1934); **A2**, 221 (1935); **A3**, 126 (1936).

(98) Krishnan, R. S.: Proc. Indian Acad. Sci. **A1**, 782 (1935).

(99) Krishnan, R. S.: Proc. Indian Acad. Sci. **A1**, 793 (1935).

(100) Krishnan, R. S.: Proc. Indian Acad. Sci. **A5**, 94, 305, 407, 499, 551, 577 (1937).

(101) Krishnan, R. S.: Proc. Indian Acad. Sci. **A7**, 91 (1938).

(102) Krishnan, R. S.: Phil. Mag. **29**, 575 (1940).

(103) Kuhn, H.: Helv. Chim. Acta **29**, 432 (1946).

(104) Kuhn, W.: Kolloid-Z. **62**, 269 (1933).

(105) Kuhn, W.: Kolloid-Z. **68**, 2 (1934).

(106) LaMer, V. K.: J. Phys. Colloid Chem. **52**, 65 (1948).

(107) LaMer, V. K., and Barnes, M. D.: J. Colloid Sci. **1**, 71 (1946).

(108) Landshoff, R.: J. Phys. Chem. **46**, 778 (1942).

(109) Landau, L., and Lifshitz, E.: *Statistical Physics*. Oxford University Press, London (1938).

(110) Landau, L., and Placzek, G.: Sowjet. Phys. **5**, 172 (1934).

(111) Lange, B.: Z. physik. Chem. **132**, 1, 27 (1928).

(112) Langevin, P.: J. phys. **7**, 249 (1910).

(113) Lauffer, M. A.: J. Am. Chem. Soc. **74**, 147 (1939).

(114) Leontovich, M.: J. Phys. (U.S.S.R.) **4**, 499 (1941).

(115) Leontovich, M.: *Statistikaya Fizika*. OGIZ, Moscow (1944).

(116) Leontovich, M., and Mandelstam, S.: Physik. Z. Sowjetunion **1**, 317 (1932).

(117) Levin, L. M.: Bull. acad. sci. U.R.S.S. (Sér phys.) **4**, 111 (1940).

(118) Lonti, R.: Mededeel. Koninkl. Vlaam. Acad. Wetenschap. Belg. Klasse Wetenschap. **6**, 5 (1944).

(119) Lorentz, H. A.: *Theory of Electrons*. Teubner, Leipzig (1909).

(120) Lotmar, W.: Helv. Chim. Acta **21**, 953 (1938).

(121) Mandelstam, L.: Ann. Physik **74**, 231 (1924).

(121a) Mark, H.: In *Frontiers of Chemistry*, Vol. 5. Interscience Publishers, Inc., New York (1948).

(122) Martin, W. H.: Proc. Roy. Soc. Canada **3** (1923).

(123) Martin, W. H., and Lehrman, S.: J. Phys. Chem. **27**, 558 (1923).

(123a) Meyer, E. H., and Ramm, W.: Physik. Z. **33**, 370 (1932).

(124) Middleton, W. E. K.: *Visibility in Meteorology*, 2nd edition. University of Toronto Press, Toronto, Canada (1941).

(125) Mie, G.: Ann. Physik **25**, 377 (1908).

(126) Möglich, F.: Ann. Physik **83**, 609 (1927).

(127) Mookerjee, B. K.: Indian J. Phys. **12**, 15 (1938).

(128) Mott, N. F., and Massey, H. S. W.: *The Theory of Atomic Collisions.* Oxford University Press, London (1933).
(129) Mott, N. F., and Jones, J.: *The Theory and Properties of Metals and Alloys.* Oxford University Press, London (1936).
(130) Mueller, H.: Phys. Rev. **50**, 547 (1936).
(131) Mueller, H.: Proc. Roy. Soc. (London) **A166**, 425 (1938).
(132) Mueller, H.: Phys. Rev. **55**, 508 (1939).
(133) Mueller, H., and Sackmann, B. W.: J. Optical Soc. Am. **32**, 309 (1944).
(134) Neugebauer, T.: Ann. Physik **42**, 509 (1943).
(135) Onsager, L.: J. Am. Chem. Soc. **58**, 1486 (1936).
(136) Ornstein, L. S., and Zernicke, F.: Proc. Roy. Acad. Sci. Amsterdam **17**, 793 (1914).
(137) Ornstein, L. S., and Zernicke, F.: Physik. Z. **27**, 761 (1926).
(138) Oster, G.: Science **103**, 306 (1946).
(139) Oster, G.: J. Colloid Sci. **2**, 291 (1947).
(140) Oster, G.: J. Gen. Physiol. **31**, 89 (1947).
(141) Oster, G.: Data to be published.
(142) Oster, G., Doty, P. M., and Zimm, B. H.: J. Am. Chem. Soc. **69**, 1193 (1947).
(143) Ostwald, W.: *Licht und Farbe in Kolloiden.* Th. Steinkopff, Dresden (1924).
(144) Paranjpe, G. R., Naik, G. Y., and Vaidya, P. B.: Proc. Indian Acad. Sci. **A9**, 333, 352 (1939).
(145) Parthasarathy, S.: Phil. Mag. **29**, 148 (1940).
(146) Perrin, F.: J. Chem. Phys. **10**, 415 (1942).
(147) Peyrot, P.: Compt. rend. **203**, 1512 (1936).
(148) Peyrot, P.: Ann. phys. **9**, 335 (1938).
(149) Pirenne, M. H.: *Diffraction of X-Rays and Electrons by Free Molecules.* Cambridge University Press, London (1946).
(150) Placzek, G.: Physik. Z. **31**, 1052 (1930).
(151) Pokrowski, G. I.: Z. Physik **41**, 493 (1927); **60**, 850 (1930).
(152) Ponder, E.: In *Medical Physics* (O. Glasser, *Editor*). The Year Book Publishers, Inc., Chicago (1944).
(153) Prins, J. A.: Trans. Faraday Soc. **33**, 110 (1937).
(154) Putzeys, P., and Brosteaux, J.: Trans. Faraday Soc. **31**, 1314 (1935).
(155) Putzeys, P., and Brosteaux, J.: Mededeel. Koninkl. Vlaam. Acad. Wetenschap. Belg. Klasse Wetenschap. **3**, 3 (1941).
(156) Ramaiah, K. S.: Proc. Indian Acad. Sci. **A5**, 138 (1937).
(157) Raman, C. V.: Proc. Indian Acad. Sci. **A14**, 228 (1941).
(158) Raman, C. V., and Krishnan, K. S.: Phil. Mag. **3**, 713 (1927).
(159) Raman, C. V., and Krishnan, K. S.: Proc. Roy. Soc. (London) **A117**, 1, 589 (1927).
(160) Raman, C. V., and Krishnan, K. S.: Phil. Mag. **5**, 498 (1928).
(161) Raman, C. V., and Ramanathan, K. R.: Phil. Mag. **45**, 213 (1923).
(162) Raman, C. V., and Ramdas, L. A.: Proc. Roy. Soc. (London) **A108**, 561 (1925).
(163) Raman, C. V., and Ramdas, L. A.: Proc. Roy. Soc. (London) **A109**, 150 (1925).
(164) Raman, C. V., and Ramdas, L. A.: Proc. Roy. Soc. (London) **A109**, 272 (1925).
(165) Raman, C. V., and Ray, B.: Proc. Roy. Soc. (London) **A100**, 102 (1921).
(166) Ramanathan, K. R.: Proc. Roy. Soc. (London) **A102**, 151 (1922).
(167) Ramanathan, K. R.: Indian J. Phys. **1**, 413 (1927).
(168) Ramdas, L. A.: Indian J. Phys. **1**, 199 (1927).
(168a) Ramm, W.: Physik. Z. **35**, 111, 756 (1934).
(169) Rao, R.: Indian J. Phys. **2**, 61 (1927).
(170) Rao, S. R.: Indian J. Phys. **2**, 7 (1927).
(171) Ray, B.: Proc. Indian Assoc. Cultivation Sci. **7**, 10 (1921); **8**, 23 (1923).
(172) Rayleigh: Phil. Mag. **41**, 447 (1871).
(173) Rayleigh: Phil. Mag. **12**, 81 (1881).

(174) Rayleigh: Phil. Mag. **49**, 324 (1900).
(175) Rayleigh: Proc. Roy. Soc. (London) **A84**, 25 (1911).
(176) Rayleigh: Proc. Roy. Soc. (London) **A90**, 219 (1914).
(177) Rayleigh: Phil. Mag. **35**, 373 (1918).
(178) Rocard, V.: J. phys. radium **4**, 165 (1933).
(179) Rosen, J. S.: J. Optical Soc. Am. **37**, 932 (1947).
(180) Rousset, A.: Ann. phys. **5**, 5 (1936).
(181) Ruedy, R.: Can. J. Research **A21**, 79, 99 (1943); **A22**, 53 (1944).
(182) Sadron, C.: J. chim. phys. **43**, 142 (1946).
(183) Schaeffer, V. J.: J. Phys. Chem. **45**, 681 (1941).
(184) Schiff, L. I.: Phys. Rev. **57**, 844 (1940).
(185) Schoenberg, E., and Lambrecht, H.: Ergeb. exakt. Naturw. **19**, 1 (1940).
(186) Shoulejkin, W.: Phil. Mag. **48**, 307 (1924).
(187) Sinclair, D.: J. Optical Soc. Am. **37**, 475 (1947).
(188) Singh, B.: Phil. Mag. **28**, 635 (1939).
(189) Singh, D.: Proc. Indian Acad. Sci. **A15**, 406 (1942).
(190) Slater, J. C., and Frank, N. H.: *Introduction to Theoretical Physics*. The McGraw-Hill Book Company, Inc., New York (1933).
(191) Slater, J. C.: *Introduction to Chemical Physics*. The McGraw-Hill Book Company, Inc., New York (1939).
(192) Smoluchowski, M.: Ann. Physik **25**, 205 (1908); Phil. Mag. **23**, 165 (1912).
(193) Speiser, R., and Brice, B. A.: J. Optical Soc. Am. **36**, 364 (1946).
(194) Stein, R. S., and Doty, P.: J. Am. Chem. Soc. **68**, 162 (1946).
(195) Stein, R. S.: Personal communication.
(196) Steubing, W.: Ann. Physik **26**, 329 (1908).
(197) Stewart, G. W.: Chem. Revs. **6**, 483 (1929).
(198) Stratton, J. A., and Houghton, H. G.: Phys. Rev. **38**, 159 (1931).
(199) Stratton, J. A.: *Electromagnetic Theory*. The McGraw-Hill Book Company, Inc., New York (1944).
(200) Strauss, U. P.: Thesis, Cornell University, 1944.
(201) Stuart, H. A., and Trieschmann, H. G.: *Hand-und Jahrbuch der chemischen Physik*, Vol. 8, Part 2. Akademische Verlagsgesellschaft, Leipzig (1936).
(202) Subbaramaija, D. S.: Proc. Indian Acad. Sci. **A5**, 138 (1935).
(203) Subrahmanya, R. S., Doss, K. S., and Rao, B. S.: Proc. Indian Acad. Sci. **A19**, 405 (1944).
(204) Svedberg, T.: *Colloid Chemistry*, 2nd edition. The Chemical Catalog Company, Inc., New York (1928).
(204a) Taylor, W. J.: J. Chem. Phys. **15**, 412 (1947).
(205) Tichanowsky, J. J.: Physik. Z. **28**, 252 (1927).
(206) Tolman, R. C.: *The Principles of Statistical Mechanics*. Oxford University Press, London (1938).
(207) Tsvetkoff, V., and Frisman, E.: Compt. rend. acad. sci. U.R.S.S. **47**, 550 (1945).
(208) Tyndall, J.: Phil. Mag. **37**, 384 (1869).
(209) Ubbelohde, A. R.: Trans. Faraday Soc. **34**, 282 (1938).
(210) van dem Borne, H.: Z. Physik **99**, 73 (1936).
(211) van der Hulst, H. C.: *Optics of Spherical Particles*. Drukkerij Duwaer and Zonen, Amsterdam (1946).
(212) Van Vleck, J. A.: Ann. N. Y. Acad. Sci. **60**, 293 (1940).
(213) Venkateswaran, C. S.: Proc. Indian Acad. Sci. **A15**, 322 (1942).
(214) Venkateswaran, R.: Trans. Chem. Soc. **121**, 2655 (1922).
(215) Volkmann, H.: Ann. Physik **24**, 457 (1935).
(216) Vrkljan, V. S., and Katalinic: Physik. Z. **37**, 482 (1936).
(217) Vuks, M. F.: Bull. acad. sci. U.R.S.S. (Sér. phys.) **9**, 192 (1945).
(218) Warren, B. E.: J. Applied Phys. **8**, 645 (1937).

(219) WASER, J., BADGER, R. H., AND SCHOMAKER, V.: J. Chem. Phys. **14,** 43 (1946).
(220) WOODS, R. W.: *Physical Optics*, 3rd edition. The Macmillan Company, New York (1934).
(221) ZERNICKE, F.: Thesis, Amsterdam, 1915.
(222) ZIMM, B. H.: J. Chem. Phys. **13,** 141 (1945).
(223) ZIMM, B. H.: J. Phys. Colloid Chem. **52,** 260 (1948).
(224) ZIMM, B. H., AND DOTY, P. M.: J. Chem. Phys. **12,** 203 (1944).
(225) ZIMM, B. H., STEIN, R. S., AND DOTY, P.: Polymer Bull. **1,** 90 (1945).
(226) ZOCHER, H., AND STIEBEL, F. S.: Z. physik. Chem. **A174,** 401 (1930).
(227) ZWETKOV, V.: Acta Physicochim. U.R.S.S. **9,** 111 (1938).

ON DOISYNOLIC ACIDS, A NEW CLASS OF ESTROGENS

K. MIESCHER

Research Laboratories, Ciba Limited, Basle, Switzerland

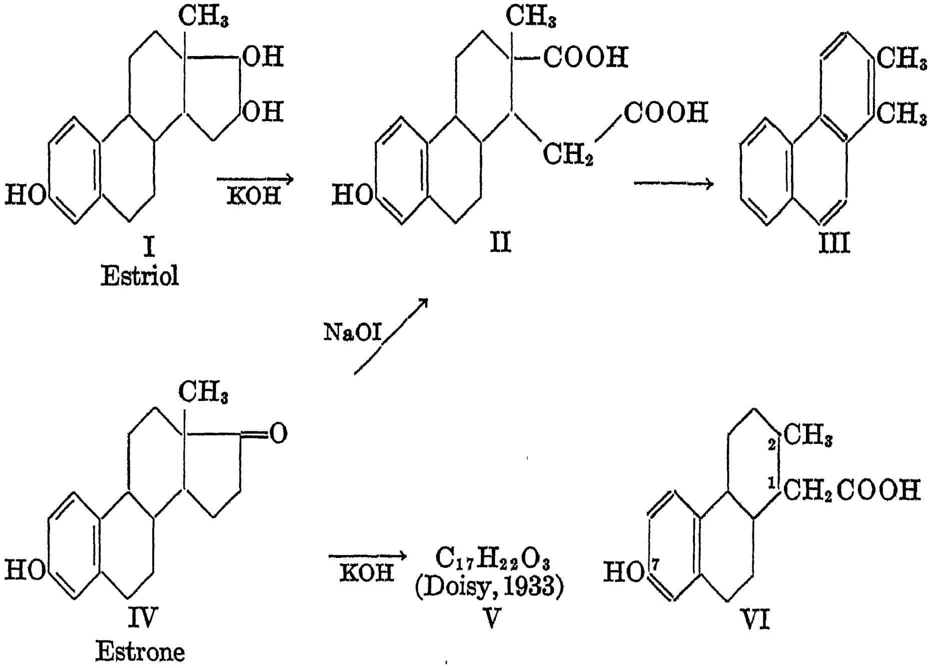
Received December 9, 1947

CONTENTS

I. Mono- and di-carboxylic acids from estrogenic hormones 367
II. Elucidation of the constitution of the monocarboxylic acids 368
III. The synthesis of bisdehydrodoisynolic acid 370
IV. The activity of the doisynolic acids 370
V. Derivatives, homologues, and analogues of α-bisdehydrodoisynolic acid 373
VI. Steric relationship between estrogenic hormones and the doisynolic acids 376
VII. "Doisynolic acids" derived from androgens 378
VIII. Monodehydrodoisynolic acids 378
IX. Total synthesis of doisynolic acids 378
X. Conclusion 383
XI. References 384

I. MONO- AND DI-CARBOXYLIC ACIDS FROM ESTROGENIC HORMONES

So far, five estrogens have been found in nature—estrone, estradiol, estriol, equilenin, and equilin—and in addition numerous synthetic ones have been prepared, which are all more or less related to stilbestrol. During the past few years we investigated a group of substances which are very closely related to the natural estrogens, and thus have collected new and interesting information on the hormone specificity problem.



In 1932 Marrian (22) succeeded in opening the five-membered ring of estriol (I) by fusion with potassium hydroxide and obtained a dicarboxylic acid which we have named "marrianolic acid" (II). Butenandt (8) converted this acid into 1,2-dimethylphenanthrol by dehydrogenation and further into 1,2-dimethylphenanthrene (III) by distillation with zinc dust, thus confirming the presumed constitution of the estrogenic hormones.

Much less attention was paid to a monocarboxylic acid (V), melting at 195°C., which was obtained by Doisy and collaborators (21) in 1933 by melting estrone (IV) with potassium hydroxide and which they believed to have the formula $C_{17}H_{22}O_3$. The American investigators first claimed that the new carboxylic acid showed several times the estrogenic activity of the starting hormone and that it was active even when given orally. However, they soon recalled this statement.

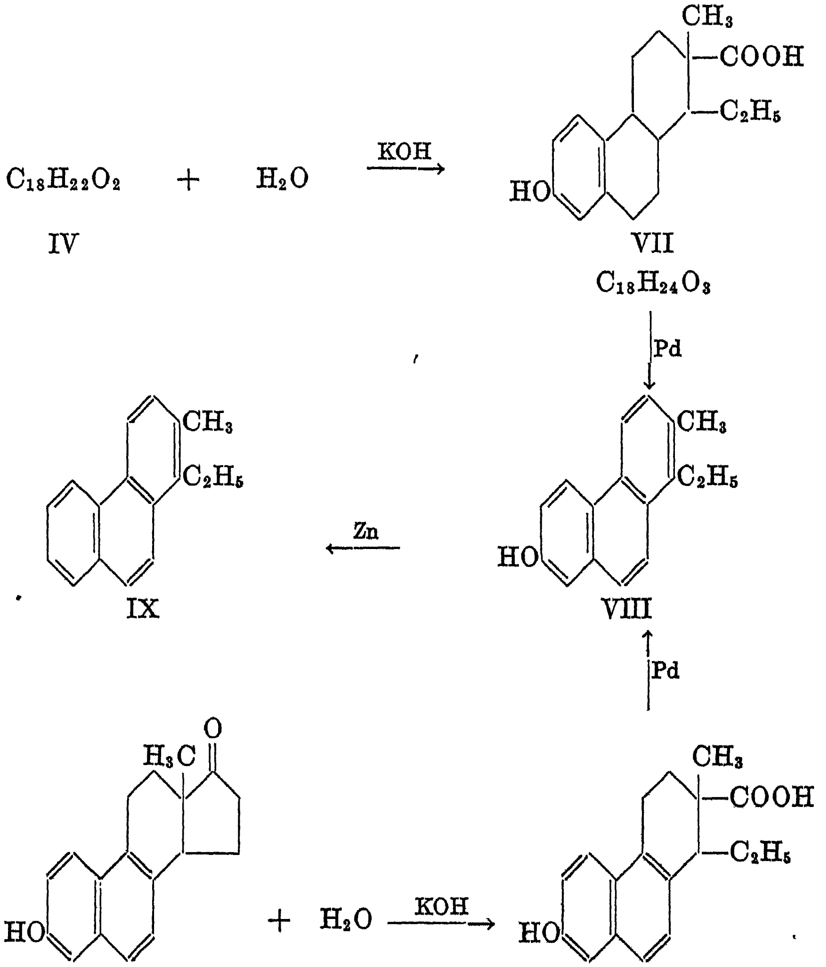
In patent applications of the Schering Company (30) dated 1937 and 1939 the question of the potassium hydroxide melt of estrogenic hormones was again taken up by Hohlweg and Inhoffen, and it was ascertained that estradiol yielded the same monocarboxylic acid as estrone. Analogous acids were also obtained from equilenin and equilin, although in a rather crude state. It is remarkable that these acids were active in rats when administered orally in doses of 1–6 γ. According to the patents the monocarboxylic acids belonged to the C_{17} series, and the acid from estrone was assigned the constitution of a 2-methyl-7-hydroxyoctahydrophenanthrene-1-acetic acid (VI).

II. ELUCIDATION OF THE CONSTITUTION OF THE MONOCARBOXYLIC ACIDS (25)

To us, the proposed formulation did not appear very likely and we decided to reinvestigate the carboxylic acids obtained from estrogenic hormones. We first prepared marrianolic acid (II) (14) and bisdehydromarrianolic acid (12) from estrone and equilenin by oxidation with hypoiodite. A study of their reactions simplified the elucidation of the corresponding monocarboxylic acids.

The first substance that we investigated in the monocarboxylic acid series was the acid from estrone (or estradiol) originally found by Doisy and which we have called "doisynolic acid" in honor of him. The fact that its ester was difficult to saponify spoke against its formulation as a hydrophenanthreneacetic acid (VI), as suggested in the German patents. Its constitution was ascertained by dehydrogenation with palladium to 1-ethyl-2-methyl-7-phenanthrol (VIII) and then by dehydroxylation with zinc to 1-ethyl-2-methylphenanthrene (IX), the latter having previously been synthesized by Haworth (11). Therefore, the formula $C_{18}H_{24}O_3$ corresponded to doisynolic acid (VII) and its formation occurred without loss of carbon by a simple hydrolytic fusion of the five-membered ring. In the case of estradiol preliminary dehydrogenation must have taken place. Similar reactions in the camphor series have been known for a long time (9, 10).

Whereas the doisynolic acid was thus obtained in a relatively simple manner in a yield of about 50 per cent, fusion of equilenin (X) with potassium hydroxide yielded a complex mixture of acids. From this mixture we were able to isolate,



X
Equilenin

XI (−)(α) m.p. 161–162°C. (*n*)
XI (+)(β) m.p. 254–256°C. (iso)

although in a poor yield, the two optically active acids α and β, owing to a difference in their acidity. Both could be dehydrogenated to the same 1-ethyl-2-methyl-7-phenanthrol (VIII) as was obtained from doisynolic acid. The two optically active acids, the α- and β-bisdehydrodoisynolic acids, were therefore diastereoisomers of the formula XI, and contained two centers of asymmetry.

Whereas no estrogenic activity can be attributed to the dicarboxylic acids, the oral threshold value of doisynolic acid in castrated female rats is 1.5 γ (compare table 1). But it is surpassed considerably by the (−)-α-bisdehydrodoisynolic acid with a threshold value of 0.05–0.07 γ, which is at least 20 times as effective as the crude acids obtained by Hohlweg and Inhoffen from equilenin. The isomeric β-acid is inactive.

We first assumed that the biologically active α-acid corresponded sterically to estrone and equilenin, and therefore designated it as the normal acid and the β-derivative as the iso acid. However, bisdehydromarrianolic acid possesses a dextrorotation, as do also equilenin, estrone, estradiol, and doisynolic acid, whereas the active α-acid is levorotatory. This will be discussed again later on in this review. It must be that during the splitting of equilenin with potassium hydroxide, a partial isomerization occurs at one of the two centers of asymmetry, C_1 or C_2, which may be attributed to the greater lability of the more strongly aromatized nucleus, since it does not occur with estrone.

III. THE SYNTHESIS OF BISDEHYDRODOISYNOLIC ACID

The elucidation of the constitution of the doisynolic acids enabled us to accomplish the total synthesis of the bisdehydro derivatives. The starting point was Cleve's acid (XII) which, according to Butenandt (7), can be transformed through a series of intermediates to β-bromoethylnerolin (XIII) and thence into 1-keto-7-methoxytetrahydrophenanthrene (XIV). Bachmann (4) in 1939 obtained from the latter 1-keto-2-methyl-7-methoxytetrahydrophenanthrene-2-carboxylic acid ester (XV). It was used by him in carrying out his elegant equilenin synthesis, which is up to now the only total synthesis of an active steroid hormone.

By reacting ethylmagnesium bromide with XV and dehydrating the resulting tertiary carbinol the ethylidene derivative (XVI) was obtained. After reduction of the double bond and demethylation of the ester and the ether groups there resulted a mixture of the two racemic bisdehydrodoisynolic acids XVIIα and XVIIβ (13).

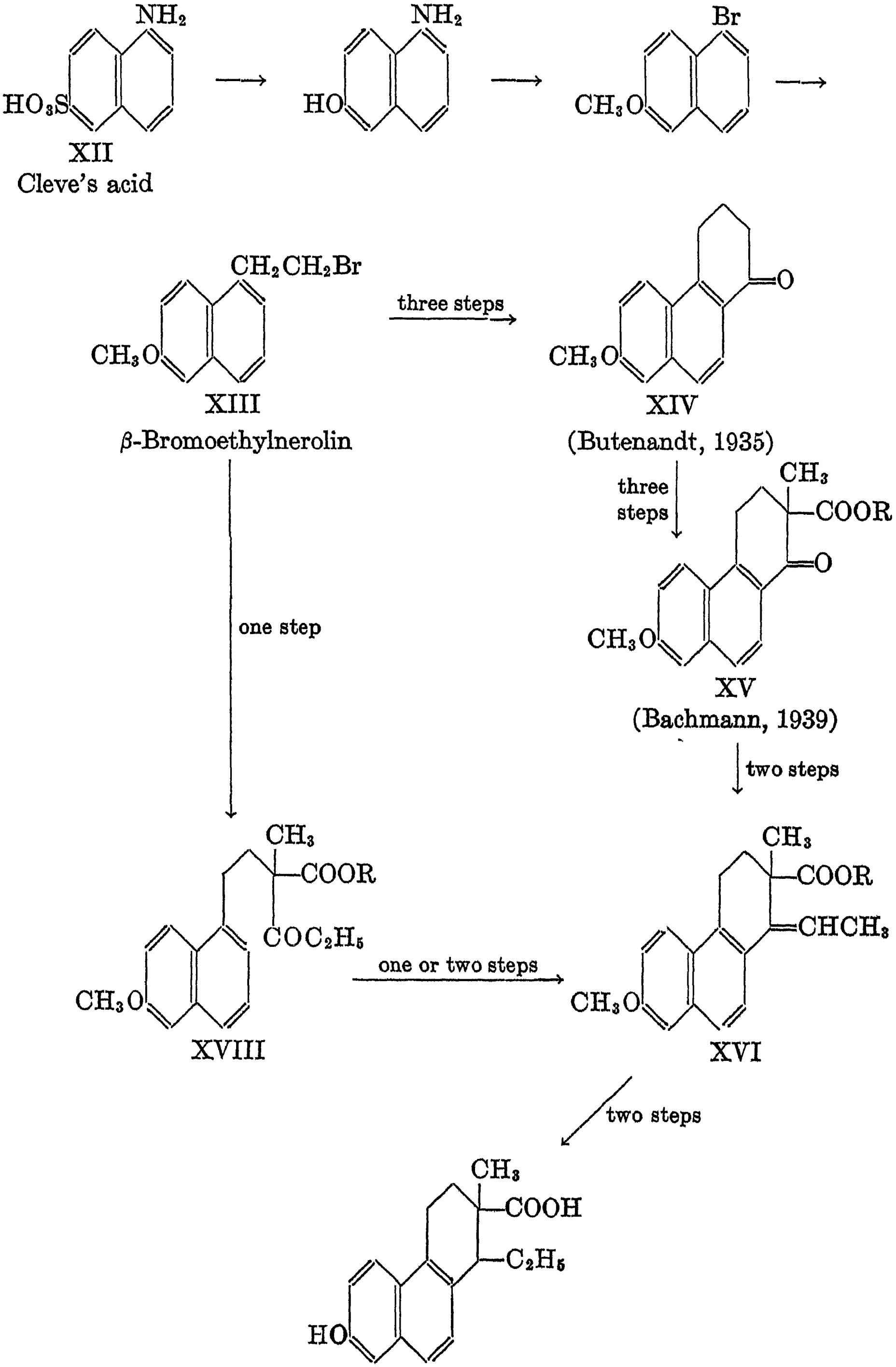
The lower-melting α-racemate (normal) proved highly active in rats, whereas the higher-melting β-racemate (iso) was ineffective. Finally, we also succeeded in separating the α-racemate into the two antipodes *via* the menthol ester (29). The levorotatory derivative was identical with the α-acid (XIα) from equilenin. The total activity of the racemate can be ascribed to this antipode.

We were able to shorten the synthesis of the acids XVII (1) from twelve steps to four steps by reacting the sodium salt of the enol of propionylpropionic acid ester with β-bromoethylnerolin and cyclizing with sulfuric acid the keto ester (XVIII) thus obtained. It is possible to carry out the hydrogenation of the ethylidene compound (XVI) in such a way that mainly the α-acid is produced.

IV. THE ACTIVITY OF THE DOISYNOLIC ACIDS

In table 1 the threshold values (32, 33) of the doisynolic acids in the estrus test on castrated rats are compared with the estrogenic hormones and diethylstilbestrol. The acids were dissolved in aqueous bicarbonate and were applied in either single or subdivided doses.

The (−)-α-bisdehydrodoisynolic acid shows the highest activity, the racemate being half as active as the levo-form. It is interesting that the activity of the 7-methyl ethers does not differ much from that of the free α-bisdehydrodoisynolic acids. Under the name "Fenocylin" the methyl ether of the α-acid has lately been submitted for clinical trials. It is interesting that the methyl ethers of some of the natural hormones exhibit a markedly lower activity: thus, the activity of estradiol methyl ether is only about 1/30th that of the free hormone.



XVII (racemic)(α) m.p. 204°C. (*n*)
XVII (racemic)(β) m.p. 235–238°C. (iso)

While the activity of the estrogenic hormones and diethylstilbestrol depends to a great extent on their mode of administration, the uniformly high activity of α-bisdehydrodoisynolic acid and its 7-methyl ether in rats is remarkable.

TABLE 1

Estrus test on castrated rats

ESTROGENS	SUBCUTANEOUS ADMINISTRATION		ORAL ADMINISTRATION
	Single dose	Five divided doses	Single dose
	Threshold values in γ		
α-Bisdehydrodoisynolic acid* (−)	0.05–0.07	—	0.05–0.07
7-Methyl ether* (−)	0.05–0.07	—	0.05–0.07
α-Bisdehydrodoisynolic acid* (racemic)	0.1–0.15	0.1–0.15	0.1–0.15
7-Methyl ether* (racemic)	0.1–0.15	0.1–0.2	0.1–0.15
β-Bisdehydrodoisynolic acid* (+)	>100	—	>100
Doisynolic acid (from estrone)* (+)	0.7–1.0	0.7–1.0	1.5
Estrone†	10–15	0.5–1.0	20–30
Estradiol†	1–2	0.3	20–30
Equilenin†	100–150	5–15	300–500
Diethylstilbestrol†	2–3	0.3–0.4	2–3

* As sodium salt, in water.

† In water.

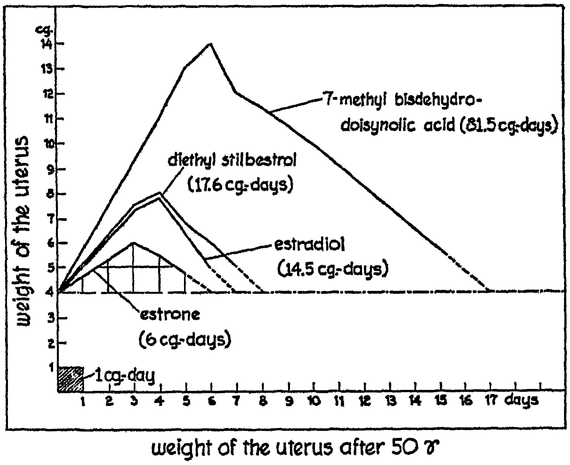


FIG. 1. Change in weight of uterus of castrated rats after administration of estrogens

The increase and decrease of the weight of the uterus of castrated rats after oral administration of a single dose of 50 γ of four different estrogens is shown in figure 1. The total activity is characterized by the area between the respective curves and a horizontal line corresponding to the initial weight of the uterus; this is the so-called "output of activity" and can be measured in cg.-days. Thus, 1 cg.-day means an increase of weight of 1 cg. maintained during 1 day. This new biological unit, which we introduced earlier, is independent of the scale chosen and when properly adapted can be advantageously used to solve many similar problems (24, 27).

The high oral activity of Fenocylin in rats enabled Meier and Tschopp (23) to determine its concentration in various organs after a single administration of 1 mg. per kilogram. A large series of animals was treated, and they were sacrificed groupwise after various intervals. The concentration in different organs was determined by feeding them to castrated rats. Table 2 shows the content of the organs after 1, 6, and 10 days. It is striking that the highest concentration was attained in the intestines, about half as much in the liver, and only about one-sixth in the uterus. This was true even when Fenocylin was given subcutaneously. Thus it was shown that the sensitiveness of the receptor organ was more important than the concentration of the drug. It is very interesting that a similar finding was recently reported by LeBlond (20). He found that after the injection of thyroxine containing radioactive iodine the main portion of the substance was located in the intestine and only about half this amount in the liver. Perhaps other biologically active acids behave in a similar manner.

TABLE 2

Concentration of methylbisdehydrodoisynolic acid (Fenocylin) in the organs of female rats in gamma per cent, after single doses of 1 mg./kg. by gastric route

ORGAN	AFTER		
	1 day	6 days	10 days
Intestines	400	27	5
Liver	130	13	2.5
Uterus	57	5–6	<1
Heart and muscles	27	2.5	1–2
Adipose tissues	13	2.2	<1
Skin	10	1	<1
Spleen	8	<1	<1
Brain	2.5	<1	<1

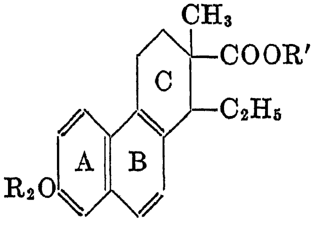
The concentration of Fenocylin in the organs of the rat quickly decreased during the first days. After 10 days only traces were detected, whereas full estrus continued much beyond that time.

Although the concentration of Fenocylin in the uterus constantly decreased, the weight of the uterus increased from 50 to 290 mg. up to the sixth day, when the amount (5–6 γ per cent) in the uterus was only about 10 per cent of the initial value. As the Fenocylin concentration fell still further, the relatively high uterus weight decreased and dropped to 170 mg. at the tenth day.

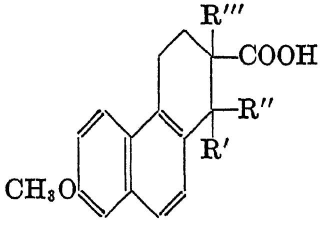
V. DERIVATIVES, HOMOLOGUES, AND ANALOGUES OF α-BISDEHYDRODOISYNOLIC ACID (26)

The total synthesis of bisdehydrodoisynolic acid gave rise to the preparation of numerous derivatives, homologues, and analogues; however, only the biological results will be discussed here.

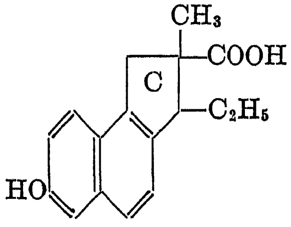
Regarding the ethers and esters (XIX) of the α-bisdehydrodoisynolic acid it might be mentioned that the higher esters, especially the 7-benzoate and the 7-butyrate of the methyl ester of the α-acid, showed the well-known ester effect as found with the natural hormones, i.e., prolonged action after injection of an oily solution.



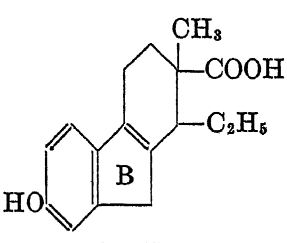
XIX



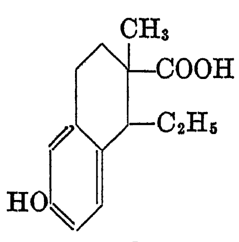
XX



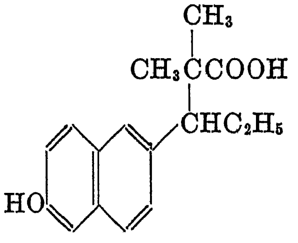
XXI



XXII



XXIIIα and XXIIIβ



XXIV

The derivatives with hydrogen or different alkyl groups at C_1 or C_2 (XX) were more interesting. In part, special methods had to be developed for their preparation. Acids without alkyl groups or with only one methyl group at C_1 or C_2 were completely or practically inactive; with two to three methyl groups or one ethyl and one methyl group at C_1 and C_2 the potency reached a maximum value with 0.1–0.2 γ. Further elongation of the side chains, however, resulted in a loss of activity. If the alkyl groups at C_1 or C_2 were closed to a five- or six-membered ring the activity disappeared. Replacement of the six-membered ring C by a five-membered ring to give the C-nor acid (XXI) had the same effect. In contrast to this, the B-normonodehydrodoisynolic acid (XXII) proved to be active, with a threshold value of approximately 1 γ.

Neither of the two diastereoisomers of the 1-ethyl-2-methyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (XXIIIα, XXIIIβ), which may be considered to be a simplified model of doisynolic acid, showed any activity. One of these isomers was also prepared by A. Horeau (17) in Paris according to our first bisdehydrodoisynolic acid synthesis.

Recently Horeau (18) has synthesized "bisdehydrodoisynolic" acids with an opened ring C. These acids belong to the naphthyl-β-propionic acid series and show estrogenic activity. He called them "allenolic acids" in honour of Allen. In figure 2 is shown the activity of the most active compound of this group, the α,α-dimethyl-β-ethyl derivative (XXIV), on castrated rats in comparison with the racemic 7-methyl ether of α-bisdehydrodoisynolic acid and diethylstilbestrol. Comparing the data for a 50 per cent response of the animals, the new acid is about one-seventh as active in the rat as Fenocylin.

It was especially interesting to substitute the carboxyl group of the α-bisdehydrodoisynolic acid by other radicals. Replacement by —CH_2COOH (XXV), —$COCH_3$ (XXVI), or —$COCH_2OCOCH_3$ (XXVII) destroyed the activity, but the aldehyde (XXVIII) and the primary carbinol (XXIX), with threshold values of 0.3–0.5 γ, were surprisingly only slightly less active than the carboxylic acid (0.1 γ). In fact, they showed a more prolonged action after subcutaneous administration. Even when the carboxyl group was replaced by a methyl group

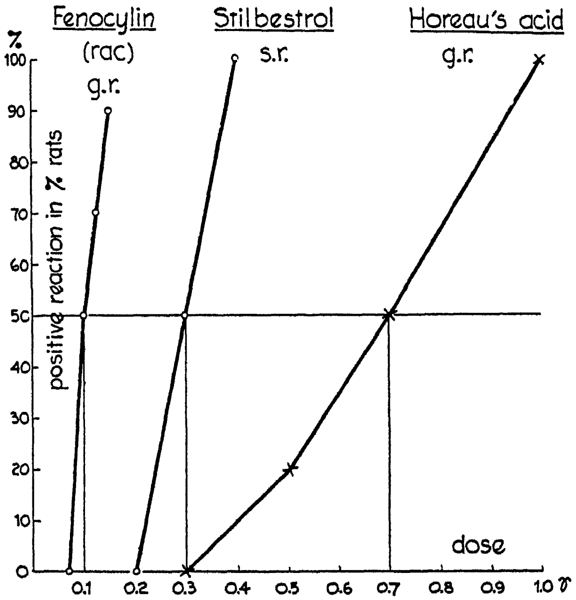
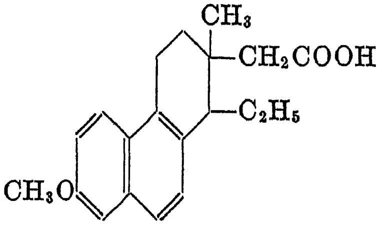
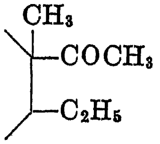


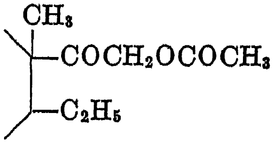
FIG. 2. Estrus test in castrated rats, each dose being applied once to ten animals. g.r = gastric route; s.r. = subcutaneous route.



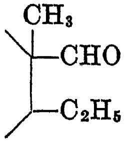
XXV



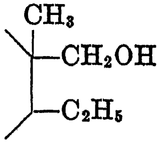
XXVI



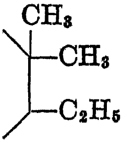
XXVII



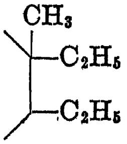
XXVIII



XXIX



XXX



XXXI

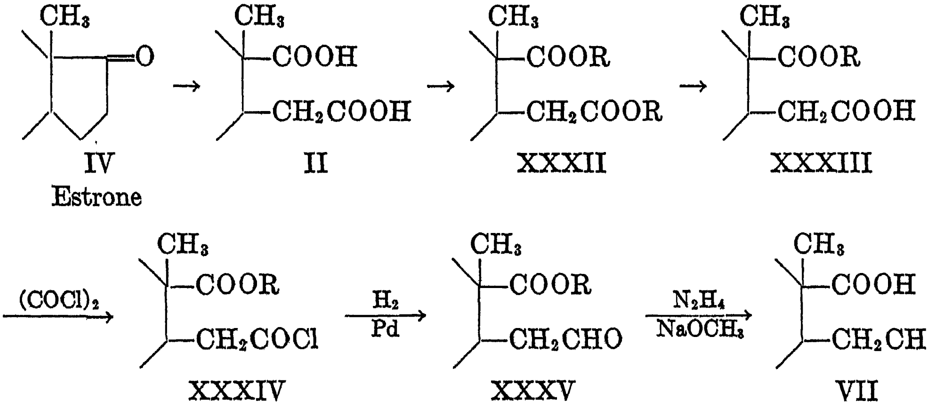
(XXX) the threshold value still attained 5–20 γ. However, the ethyl derivative (XXXI) was inactive.

The fact that the carboxylic acid and the corresponding carbinol show about the same physiological activity has also been observed in connection with vitamin A, with pantothenic acid, and perhaps with oxybiotin. Probably oxidation of the carbinol or aldehyde group occurs in the organism.

VI. STERIC RELATIONSHIP BETWEEN ESTROGENIC HORMONES AND THE DOISYNOLIC ACIDS (15)

As has already been shown, two diastereoisomeric bisdehydrodoisynolic acids are formed from equilenin by fusion with potassium hydroxide, the levorotatory "normal" or α-acid, and the dextrorotatory "iso" or β-acid. Since fusion with potassium hydroxide is a very drastic reaction which obviously is responsible for the partial rearrangement of the substituent at C_1, we searched for a more unequivocal series of reactions.

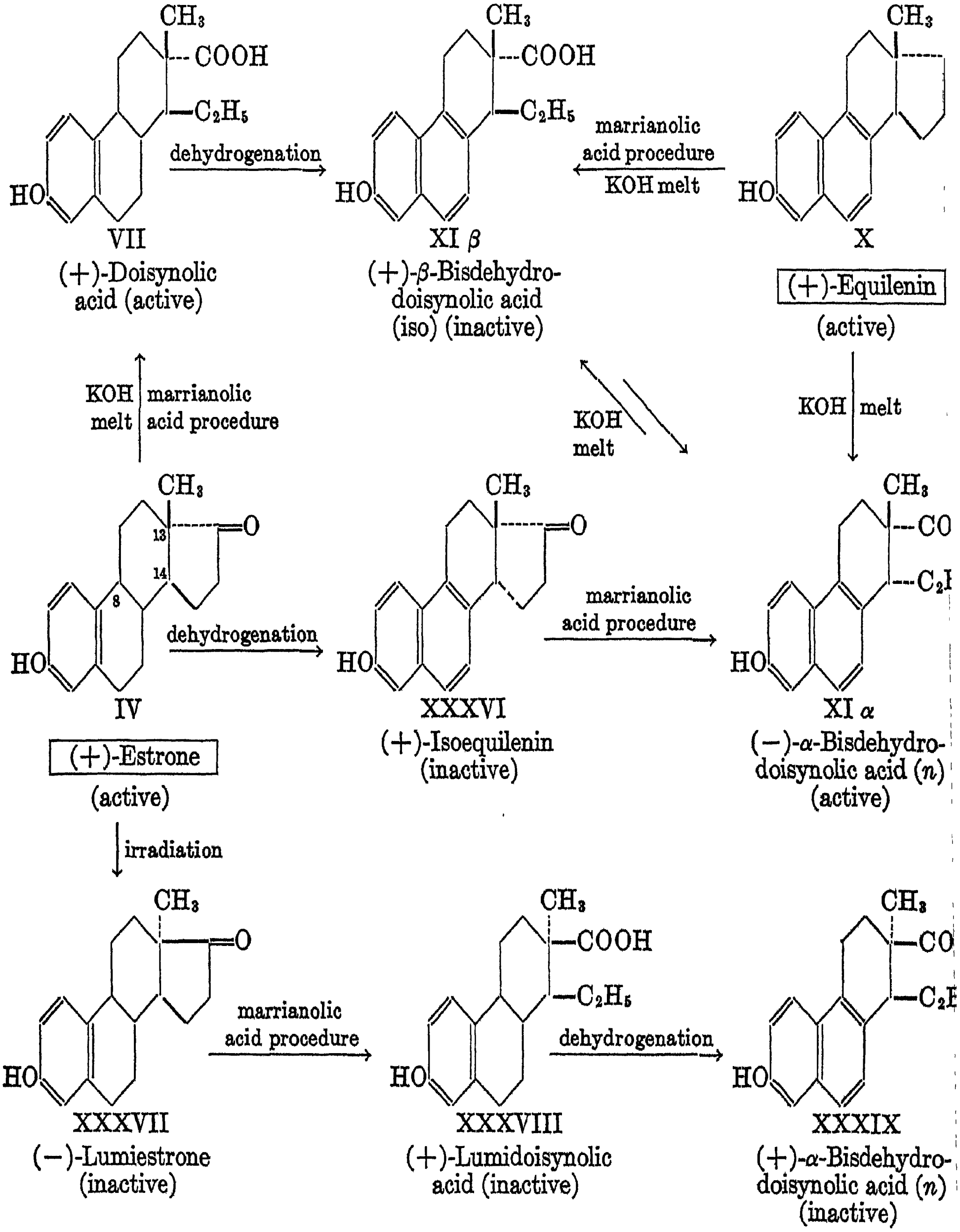
Such a one is the stepwise transformation of estrone (IV) *via* marrianolic acid



(II) and the intermediates XXXII to XXXV to the same dextrorotatory doisynolic acid (VII) as was obtained by the alkali hydroxide fusion of estrone. However, with the same procedure the active (+)-equilenin (X) led to the inactive (+)-β-bisdehydrodoisynolic acid (iso) (XIβ) and the inactive (+)-isoequilenin (XXXVI) to the active (−)-α-bisdehydrodoisynolic acid (normal) (XIα). In the latter case the change in rotation occurs during the formation of the respective bisdehydromarrianolic acid, obviously without change of configuration.

By irradiation of estrone (IV) rearrangement occurs at C_{13}, leading to lumiestrone (XXXVII). This was transformed by the marrianolic acid procedure to (+)-lumidoisynolic acid (XXVIII), which on dehydrogenation gave the dextrorotatory inactive antipode of α-bisdehydrodoisynolic acid (XXXIX).

The reduction of the monoaldehydes, which in the marrianolic acid procedure are obtained as intermediate products, with hydrazine hydrate in the presence of sodium methoxide at 190°C. by the method of Wolff–Kishner does not, however, quite exclude rearrangements. For example, we have found that the α- and β-bisdehydrodoisynolic acids may be converted into each other to a certain extent by heating with aqueous alkali hydroxide.



VII
(+)-Doisynolic acid (active)

XI β
(+)-β-Bisdehydrodoisynolic acid (iso) (inactive)

X
(+)-Equilenin
(active)

IV
(+)-Estrone
(active)

XXXVI
(+)-Isoequilenin (inactive)

XI α
(−)-α-Bisdehydrodoisynolic acid (n) (active)

XXXVII
(−)-Lumiestrone (inactive)

XXXVIII
(+)-Lumidoisynolic acid (inactive)

XXXIX
(+)-α-Bisdehydrodoisynolic acid (n) (inactive)

--- = bond in α-position; — = bond in β-position.

Recently we were able to confirm our former result by boiling the mercaptal of the (+)-β-bisdehydromarrianolic monoaldehyde with nickel in alcoholic solution. The steric relationship was further corroborated by mild dehydrogenation of (+)-doisynolic acid (VII) in the form of its ether-ester to the inactive (+)-β-bisdehydrodoisynolic acid derivative (XIβ). Previously Butenandt (6) had obtained the (+)-isoequilenin (XXXVI) from estrone (IV) in a similar manner, but in this case inversion took place at C_{14}, in the α-position to the naphthalene ring.

Provided that rings C and D are *trans* in both estrone and equilenin, as is assumed in our formulas, it seems now well established that in doisynolic acid the carboxyl and ethyl groups are correspondingly in the *trans* position, while in the highly active (−)-α-bisdehydrodoisynolic acid they are in the "unnatural" *cis* position.

VII. "DOISYNOLIC ACIDS" DERIVED FROM ANDROGENS (16)

In attempting to answer the question as to whether there also exist any "doisynolic acids" which exhibit androgenic activity, a similar change of androgenic hormones suggested itself. Direct fusion with potassium hydroxide was out of the question in this case, but the stepwise transformation *via* the dicarboxylic acids led to the desired compounds.

Starting from dehydroisoandrosterone (XL), our procedure is illustrated by formulas XLI to XLV.

The intermediate "marrianolic acid" (XLI) (34) is related to the etiobilienic acid of Wieland. The new, purely hydroaromatic "doisynolic acids" (XLII to XLV) may be considered as analogues of dehydroandrosterone, of androstenedione, or of testosterone, as well as of isoandrosterone and androstanedione. Unfortunately, they were completely inactive in androgenic and estrogenic tests.

VIII. MONODEHYDRODOISYNOLIC ACIDS (2)

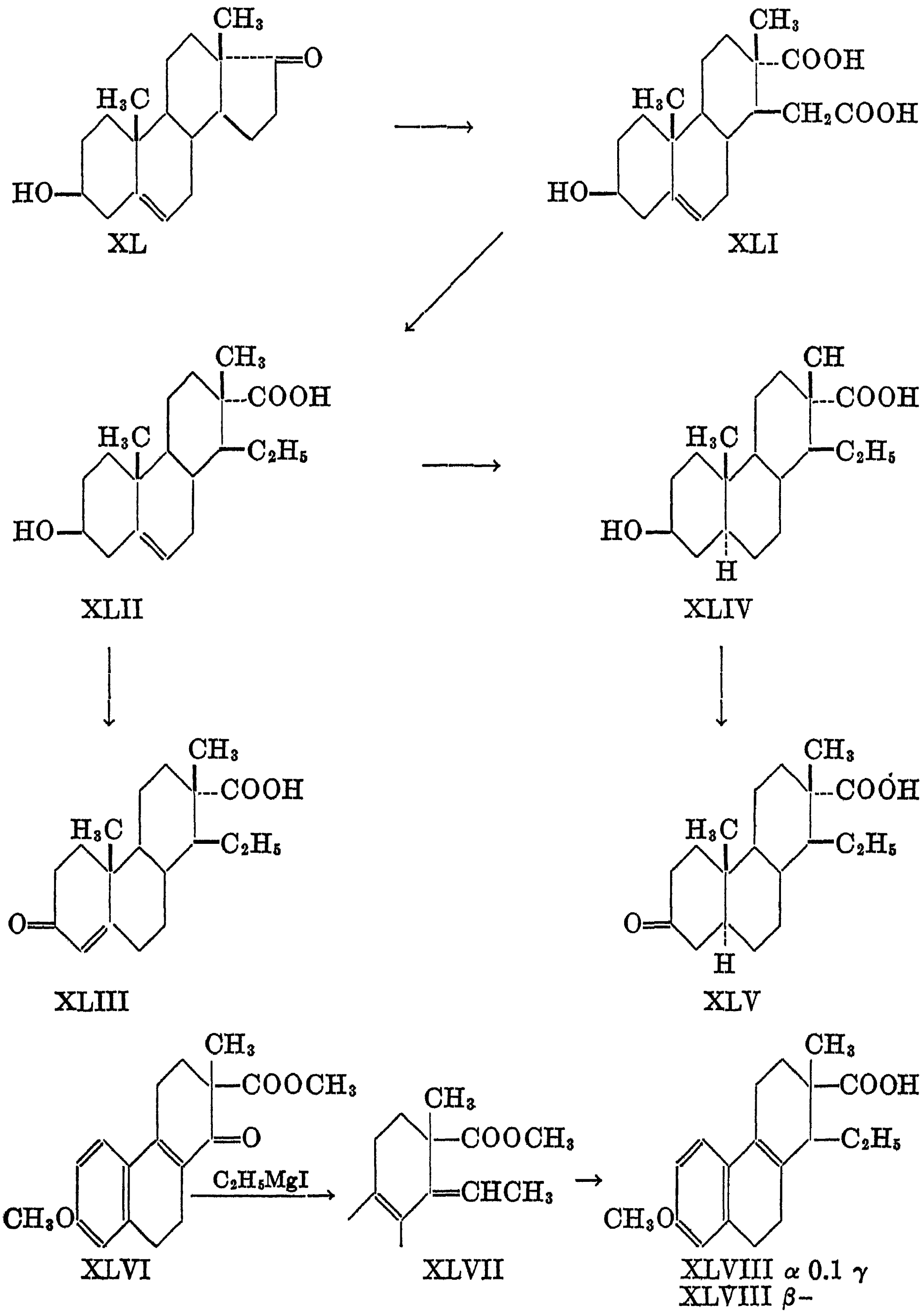
We also were interested in the total synthesis of those doisynolic acids which are di- or tetra-hydrogenated in ring B. The preparation of monodehydrodoisynolic acids with a ditertiary double linkage did not present particular difficulties, as the number of possible isomers is not greater than in the case of the bisdehydrodoisynolic acids. However, we found that the partially hydrogenated ring had a great tendency to turn into the purely aromatic ring.

We started our synthesis with the hexahydrophenanthrene-β-ketocarboxylic acid ester (XLVI), already obtained by Bachmann and coworkers (5) in 1942 in their attempt to prepare natural estrone. By proceeding *via* the ethylidene derivative (XLVII) we obtained two diastereoisomeric 7-methylmonodehydrodoisynolic acids (XLVIIIα) and (XLVIIIβ), of which the lower-melting α-acid had an oral threshold value in rats of 0.1 γ. It proved to be as effective as the racemic α-bisdehydrodoisynolic acid.

Sterically the highly active α-monodehydrodoisynolic acid corresponds to the equally active α-bisdehydrodoisynolic acid into which it can be converted by dehydrogenation of its ether-ester with palladium.

IX. TOTAL SYNTHESIS OF DOISYNOLIC ACIDS (3)

The doisynolic acid from estrone contains four centers of asymmetry. Sixteen isomers and eight racemates are possible. As was to be expected, undesirable

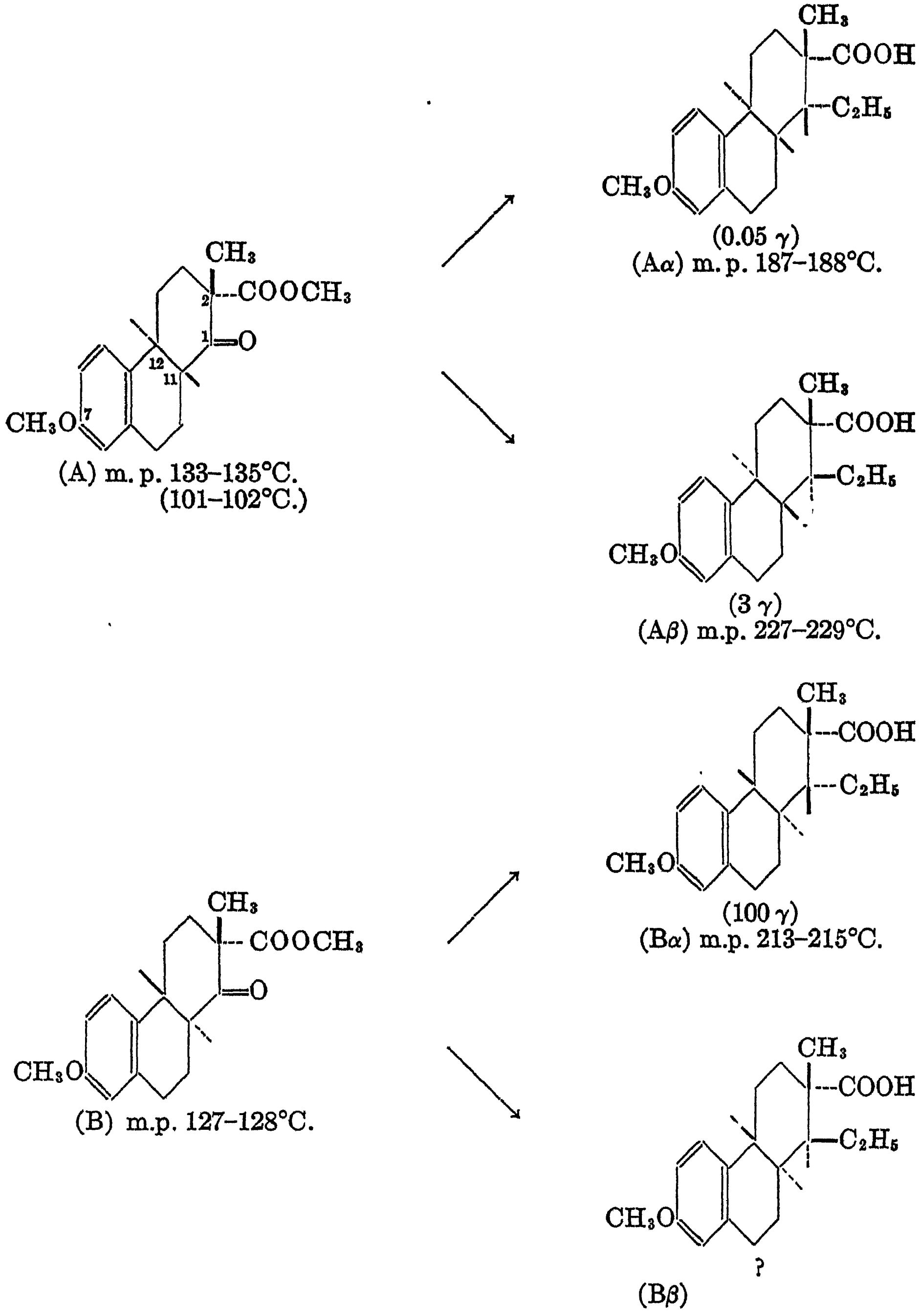


mixtures were formed by the catalytic hydrogenation of the mono- and bis-dehydrodoisynolic acids; this also follows from similar experiments of the American workers Hunter and Hogg (19).

Owing to a method recently recommended by R. Robinson, the action of sodium on the 7-methylether-2-methylester-α-monodehydrodoisynolic acid (ester

*Keto esters**
XLIX

*Doisynolic acids**
L



(A) m. p. 133–135°C.
(101–102°C.)

(0.05 γ)
(Aα) m.p. 187–188°C.

(3 γ)
(Aβ) m.p. 227–229°C.

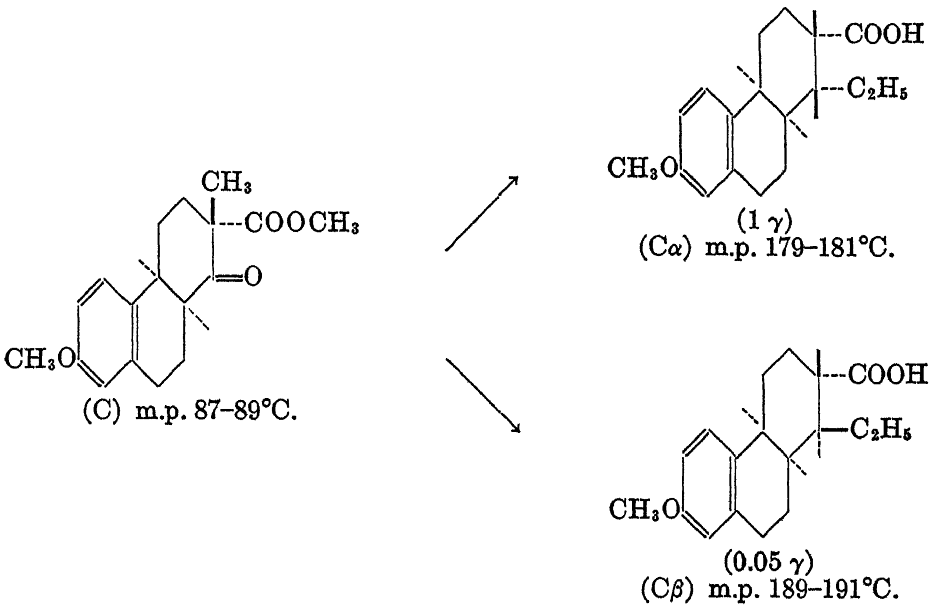
(B) m.p. 127–128°C.

(100 γ)
(Bα) m.p. 213–215°C.

?
(Bβ)

---

*The racemic methyl ethers are characterized here by the formula of only one of the enantiomers. To each formula therefore is to be added its antipode. The melting points (in °C.) and the threshold values (by gastric route) are those of the racemates.



(C) m.p. 87–89°C.

(1 γ)
(Cα) m.p. 179–181°C.

(0.05 γ)
(Cβ) m.p. 189–191°C.

of XLVIIIα) in a mixture of alcohol and liquid ammonia has enabled us to reduce the ditertiary double bond in such a manner that, after saponification of the reaction mixture, two racemic 7-methyldoisynolic acids of melting point 187–188°C. and 213–215°C., respectively, were obtained in a crystalline state, although in a poor yield. The lower-melting racemic acid with a stomachal threshold value of 0.05 γ proved to be about 30 times more effective than the "natural" (+)-doisynolic acid from estrone. The higher-melting one, however, was almost inactive.

Robinson and Walker (28) in 1936, and later Bachmann and collaborators (5) in their attempt to obtain natural estrone by total synthesis, had already prepared 1-keto-2-methyl-7-methoxyoctahydrophenanthrene-2-carboxylic esters (XLIX). They possess three centers of asymmetry, and accordingly four racemates are possible. The British as well as the American research workers obtained the keto esters only as oily mixtures. We have been able to isolate three racemic methyl esters A, B, and C (XLIX) of the four possible ones in a pure crystalline state. A fourth crystallizate proved to be dimorphic with A.

By methods which we had formerly developed it is theoretically possible to convert each of these keto esters into two racemic doisynolic acids α and β (L), one with the ethyl and carboxyl groups in the *cis* position and the other with these groups in the *trans* position. So far we have prepared five of these acids.

Acid Aα (L), derived from keto ester A, was identical with the highly active acid from the hydrogenation of the ester of acid XLVIIIα and acid Bα with the inactive one. Both of these doisynolic acids were dehydrogenated to α-bisdehydrodoisynolic acid; therefore the ethyl and the carboxyl groups must have been in the *cis* position. Acid Aβ was dehydrogenated to β-bisdehydrodoisynolic acid. It should be the racemate of doisynolic acid from estrone, and it was just half as active. Also, their mixture showed no depression of melting point. In fact, by fractional crystallization of the cholesterol ester of Aβ we were able to obtain the (−)-antipode of the "natural" acid, which showed the same melting point, but opposite rotation.

While in the less hydrogenated doisynolic acids the activity was restricted to the *cis* forms, in the octahydrogenated A acids both diastereomers proved to be active; however, the *cis* form surpassed the *trans* form by sixty times.

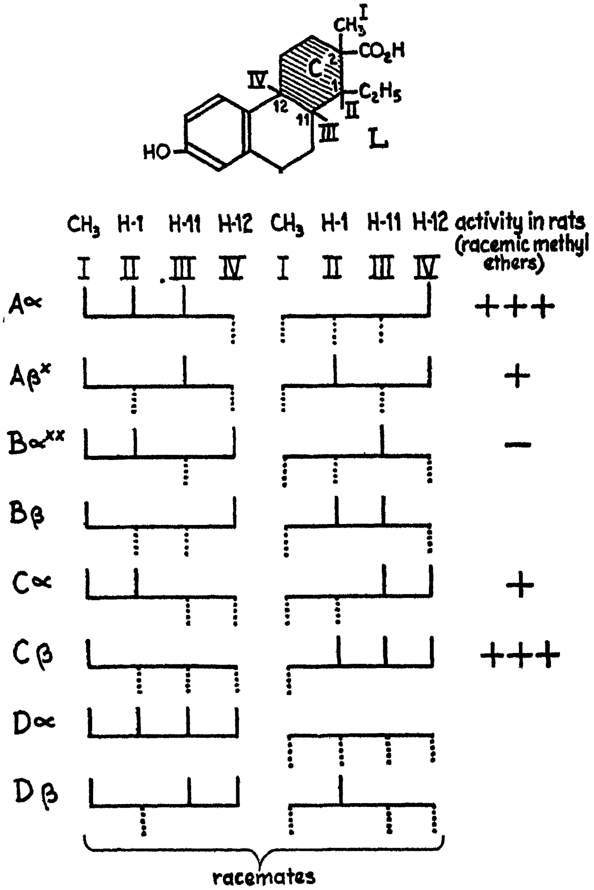


FIG. 3. Steric relationship in doisynolic acids. x = "natural" acid; xx = "lumi" acid.

The mixture of (+)-lumidoisynolic acid with L-Aα or -Cα shows a definite depression of melting point, but not with -Bα; therefore, L-Bα is probably the racemic form of lumidoisynolic acid.

Since the keto ester C (XLIX) can be transformed into the keto ester A, for instance by alkali, we assume that inversion takes place at C_{11} in the α-position to the keto group. Both acids Cα and Cβ (L) proved to be highly active but in this case the *trans* isomer Cβ, with an activity similar to that of the acid Aα, surpassed the *cis* form by about twenty times.

Figure 3 gives a short survey of the steric relationship between all possible doisynolic acids (L). Only ring C containing all four centers of asymmetry is taken into consideration. The methyl group at C_2 and the hydrogen atoms at C_1, C_{11}, and C_{12} are numbered from I to IV. By projecting ring C to a plane vertical to its own, it is represented simply by a straight line. Substituents in the β-position (over the plane) are indicated by vertical full lines above the straight line and those in the α-position (under the plane) by dotted lines below.

Until now only those acids have proved to be active in which the substituents I and IV or 2-methyl and 12-hydrogen were in the *trans* position (as presumably in estrone). So the unknown acids Bβ and Dα and Dβ ought to be inactive or only slightly active, considering the *cis* position of the groups I and IV. From the active pairs of acids A and C those isomers (Aα and Cβ) with the hydrogens II and III in the *cis* position showed the higher activity. The same scheme may also be employed to represent the steric relationship of the isomers of estrone and a similar scheme can be used for the representation of steroids with still more asymmetric centers. An example of this is 3(α),17(β)-androstanediol

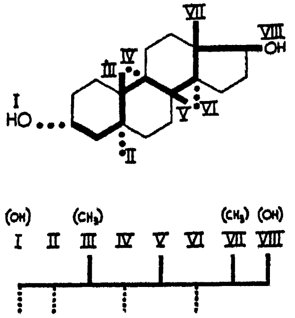


FIG. 4. 3(α),17(β)-Androstanediol (LI)

(LI), in which the centers of asymmetry are presumably as shown in figure 4.

We initially doubted the corresponding configuration of equilenin and estrone, owing to the difference in the activity of the respective monocarboxylic acids. However, this apparent inconsistency, recently also discussed by Shoppee (31), is now believed to have disappeared.

X. CONCLUSION

Our investigations starting with the monocarboxylic acid from estrone, which Doisy prepared fifteen years ago, have led to the discovery of a large class of new, highly active estrogens. They are so closely related to the natural hormones that it is interesting to speculate as to whether acids of this kind might not occur in nature; however, there is no evidence for this as yet.

It is a very curious fact that on the one hand estrogenic activity is maintained independently of whether ring D or both rings C and D of the estrogenic hormones are opened, or of whether the ring ketone or hydroxyl group is replaced in the opened forms by a carboxyl, an aldehyde, or a carbinol group; yet on the other hand, the activity is closely restricted to the presence of certain alkyl groups and especially to definite spatial configurations. So it is only natural to look for an explanation for the established relationship between estrogenic activity and structure.

Unfortunately, we shall not be able to find such an explanation until we know more about the character of the receptor or receptors within the organism and of the processes involved in the action of the estrogens. A vast unexplored field lies ahead of us, and we can only hope that physiologists and biochemists will soon make successful advances.

XI. REFERENCES

(1) Anner, G., and Miescher, K.: Helv. Chim. Acta **29**, 586 (1946).

(2) Anner, G., and Miescher, K.: Experientia **2**, 409 (1946); Helv. Chim. Acta **29**, 1889 (1946).

(3) Anner, G., and Miescher, K.: Helv. Chim. Acta **30**, 1422 (1947).

(4) Bachmann, W. E., Cole, W., and Wilds, A. L.: J. Am. Chem. Soc. **61**, 974 (1939); **62**, 824 (1940).

(5) Bachmann, W. E., Kushner, S., and Stevenson, A. C.: J. Am. Chem. Soc. **64**, 974 (1942).

(6) Butenandt, A., *et al.*: Ber. **74**, 1308 (1941); **75**, 1931 (1942).

(7) Butenandt, A., and Schramm, G.: Ber. **68**, 2083 (1935).

(8) Butenandt, A., Weidlich, H. A., and Thompsen, H.: Ber. **66**, 601 (1933); J. Soc. Chem. Ind. (London) **52**, I, 289 (1933).

(9) Delalande, Z.: Ann. **38**, 337 (1841).

(10) Guerbet, M.: Compt. rend. **147**, 70 (1908).

(11) Haworth, R. D.: J. Chem. Soc. **1934**, 460.

(12) Heer, J., Billeter, J. R., and Miescher, K.: Helv. Chim. Acta **28**, 991 (1945).

(13) Heer, J., Billeter, J. R., and Miescher, K.: Helv. Chim. Acta **28**, 1342 (1945).

(14) Heer, J., and Miescher, K.: Helv. Chim. Acta **28**, 156 (1945).

(15) Heer, J., and Miescher, K.: Helv. Chim. Acta **29**, 1895 (1946).

(16) Heer, J., and Miescher, K.: Helv. Chim. Acta **30**, 786 (1947).

(17) Horeau, A., and Jacques, J.: Compt. rend. **222**, 961 (1946).

(18) Horeau, A., and Jacques, J.: Compt. rend. **224**, 862 (1947).

(19) Hunter, J. H., and Hogg, J. A.: J. Am. Chem. Soc. **68**, 1676 (1946).

(20) LeBlond, C. P.: Communication at the Laurentian Hormone Conference of September 8–12, 1947.

(21) MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A.: J. Biol. Chem. **99**, 327 (1933); **101**, 753 (1933); U. S. patent 2,069,096 (1933).

(22) Marrian, G. F., and Haslewood, G.: J. Soc. Chem. Ind. (London) **51**, II, 279 T (1932).

(23) Meier, R., and Tschopp, E.: Experientia **2**, 141 (1946).

(24) Miescher, K.: Schweiz. med. Wochschr. **68**, 1345 (1938).

(25) Miescher, K.: Helv. Chim. Acta **27**, 1727 (1944); Experientia **2**, 237 (1946).

(26) Miescher, K., *et al.*: Helv. Chim. Acta **29**, 859 (1946); **30**, 413, 544 (1947).

(27) Miescher, K., Scholz, C., and Tschopp, E.: Biochem. J. **32**, 141 (1938).

(28) Robinson, R., and Walker, J.: J. Chem. Soc. **1936**, 747.

(29) Rometsch, R., and Miescher, K.: Helv. Chim. Acta **29**, 1231 (1946).

(30) Schering A.-G., Berlin (W. Hohlweg and H. H. Inhoffen): German patents 705,862 (1937) and 719,572 (1939).

(31) Shoppee, C. W.: Nature **160**, 64 (1947).

(32) Tschopp, E.: Schweiz. med. Wochschr. **74**, 1310 (1944); **76**, 1166 (1946).

(33) Tschopp, E.: Helv. Physiol. Pharmacol. Acta **4**, 271, 401 (1946).

(34) Wettstein, A., Fritzsche, H., Hunziker, F., and Miescher, K.: Helv. Chim. Acta

RELATIONSHIPS BETWEEN ABSORPTION SPECTRA AND CHEMICAL CONSTITUTION OF ORGANIC MOLECULES

LLOYD N. FERGUSON

Department of Chemistry, Howard University, Washington 1, D.C.

Received February 14, 1947

A brief historical account of theories concerning the origin of color in organic compounds is given. Correlations between the wave length of absorption bands and the chemical constitution of organic molecules are reviewed and present-day quasi "classical quantum-mechanical" concepts on color are discussed. The influence on color of such factors as resonance, steric hindrance, the conjugation and insulation of chromophores, and linearly conjugated chromophores is illustrated. The effects of stereostructural changes on the position and the number of absorption bands are described. Several quantitative relationships between the wave length of the maximum absorption band and chemical constitution are presented.

CONTENTS

I. Introduction 385
II. Historical background 387
III. Theory of absorption of light 390
IV. Resonance and color 395
V. Conjugation and insulation of chromophores 397
VI. Spectra of compounds containing two conjugated chromophores 401
VII. Linearly conjugated systems 406
VIII. Steric hindrance and color 419
IX. Chemical constitution and the shape of spectra 423
  A. Fine structure 424
  B. Partials 428
  C. *y*-Bands 429
  D. *z*-Bands 434
  E. *x*′-Bands 435
X. Summary 439
XI. References 440

I. INTRODUCTION

One of the long-range goals of organic chemists has been the determination of the chemical constitution of organic substances from a study of their physical properties and, conversely to a limited degree, the prediction of certain physical properties of organic substances from a knowledge of their structure. One such physical property is color as recorded by the measurement of absorption spectra. For over three-quarters of a century, organic chemists have been studying the color and structure of organic compounds and have drawn a large number of qualitative and, more recently, quantitative correlations between them. Several theories to interpret absorption spectra have been proposed; however, few have been of sufficient generality to apply to more than one or two classes of dyes.

It has been difficult for organic chemists through classical theories to learn just what causes color in organic substances. With the application of quantum mechanics the chemical physicists[1] have been more successful in this direction. As a result of qualitative and semiempirical quantitative applications of approximation methods much is now understood about the absorption peaks in terms of the characteristic electronic energy levels of various atomic groupings. It is now possible to calculate the frequencies and, in some instances, the intensity of light absorbed by simple molecules, and to obtain values which agree remarkably well with the experimental ones. Eventually, the same may be possible for all substances. There are several reasons,[2] however, why organic chemists should, in the meantime, continue their search for correlations between molecular structure and spectra until, through a fusion of empirical and theoretical methods, it will be possible to define all the laws for the absorption of light by organic molecules. For instance, qualitative relationships between the color and the chemical constitution of organic molecules serve as a wieldy tool to elucidate the structure of and to characterize new compounds. Many cases are found in the literature where the structure of a compound was selected from among several possibilities on the basis of its absorption spectra. In this respect, Jones (140) has found that systems of condensed aromatic rings have associated with them a characteristic spectrum by means of which a particular ring system may be recognized. Further, an accurate compilation of quantitative data on the spectra of pure compounds will provide material for the quantum theorists.

Although a large number of more or less detailed reviews (4, 34, 52, 75, 114, 133, 189, 190, 195, 201, 212, 228, 249, 266, 295, 304) have appeared on this subject, Lewis and Calvin (182) have probably given the most general semiclassical treatment[3] of the absorption of light by organic substances. For complete understanding,[4] fluorescence, phosphorescence, and the emission of light should be considered over the spectral range from the vacuum ultraviolet to the far infrared. However, this article will be limited to the absorption of light of wave lengths between 200 mμ and 800 mμ.

[1] See, particularly, the publications by Mulliken (217, 220, 221), Forster (91), Sklar (277), Hückel (128), Price (239), Sponer (282), Herzfeld (120, 121), Bowen (31), Pauling (226), and London (196).

[2] Concerning the application of spectrophotometry in qualitative and quantitative analyses and in physicochemical investigations see references 22, 34, 39, 56, 111, 153, 213, 242, 258, 260, and 293.

[3] For a brief presentation see the discussion given by Branch and Calvin (32, pages 159 to 182).

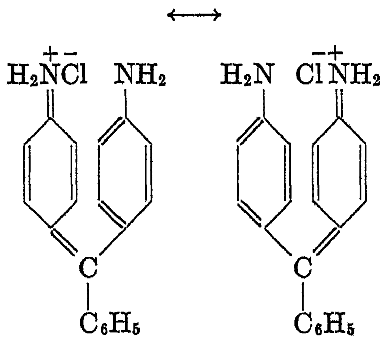
[4] The definitions of some useful spectrographic terms are as follows: *hyperchrome* = a group which causes an increase in the molecular extinction coefficient of an absorption band; *hypochrome* = a group which causes a decrease in the molecular extinction coefficient of an absorption band; *bathochrome* = a group which produces a shift of an absorption band toward longer wave lengths; *hypsochrome* = a group which produces a shift of an absorption band toward shorter wave lengths; *chromophore* = a group containing multiple bonds which are fundamentally responsible for the color of organic substances (Gr. *chroma*, color, + *phoros*, bearer); *auxochrome* = a group which does not confer color upon an otherwise colorless substance but does increase the coloring power of a chromophore (Gr. *auxo-*, increase).

II. HISTORICAL BACKGROUND

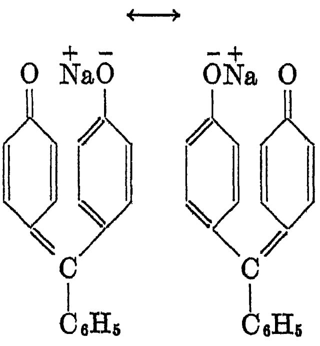
Graebe and Liebermann (99) were probably the first to report that there existed a relationship between the color and the chemical constitution of organic molecules. A few years later, in 1876, Witt (303) stated that for a substance to exhibit color its structure must possess unsaturated linkages such as C=C, N=O, etc., to which he gave the term "chromophore" (54, 55, 194), and that the color of such compounds is enhanced when they possess, in addition, certain groups such as NO_2, NH_2, or OH, which he called "auxochromes" (2, 55, 147). In 1879, Nietzki (223) formulated an empirical rule to which reference is still made occasionally by some authors: namely, that the colors of related compounds deepen with increasing molecular weights (color depth increases in going from yellow through red to green; that is, the complementary colors of the spectral ranges, violet to red). A simple example of an exception to this rule is the fact that alkylbenzenes, with alkyl groups containing from one to six carbon atoms, all have their maximum absorption bands at 269 $m\mu$ (229).

About this time there began to appear a series of theories attributing color to some type of valency change in the molecule. In 1888, Armstrong (7) proposed that all colored compounds contain a quinoid structure, or one that is changeable into such. Hewitt (123) showed that the color is deeper the longer is the conjugated system. In 1906, Baly (10) and his coworkers expressed the belief that color is due to a dynamic isomerism between atoms that are in the proper positions; they called this isomerism "isorropesis." This same idea was expressed in different words by Kauffmann (147), who ascribed color to the shattering of the principal valencies of the atoms and their resolution into scattered component forces, and also by Hantzsch (102), who attributed color to changes in the distribution of affinity without accompanying changes in the relative positions of atoms, a phenomenon which he called valency isomerism. Baly (11) stressed the idea that color is due not to a change in structure but to an opening up of the molecular fields of force.

Through this era there was a common belief, first advanced by Hartley (105), that absorption bands are characteristic of the parent compound and are merely altered by chromophores, auxochromes, or substituents. Overlapping this period with that of the next is the work of Baeyer (9), who stated in 1907 that the color of triphenylmethane dyes is due to an oscillating atom.

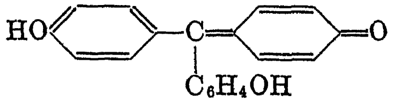


and

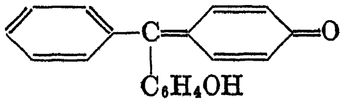


In 1913, Campbell (60) attributed the absorption of light to vibrating electrons, and in 1914, Adams and Rosenstein (1) stated that it may be due to either oscillating electrons or charged particles, such as ions. In 1916 Lewis (177), and later Wells (298), also attributed the absorption of light to electronic vibrations, while Meek (205) tried to determine the number of vibrating electrons. Baly (12) applied the old quantum theory of Bohr to absorption spectra and attempted to calculate absorption bands in the ultraviolet from bands in the infrared.

This period introduced the present-day belief that oscillating electrons within a molecular structure permit the absorption of light by the substance. Several proposals were advanced in the attempt to explain or describe these electronic vibrations in classical terms.[5] In 1921, Moir (211) postulated that color in organic substances is due to electrons revolving in oval orbits about the whole molecule with a period equal to that of the wave length of light absorbed by the colored substance. He stated that substitutions in a particular molecule affect the wave length of its maximum absorption band by altering the size of this orbit. From the wave length, λ_0, of the maximum absorption band of a reference molecule the absorption band for other substances λ_x, can be calculated by multiplying the fundamental wave length, λ_0, by substitution and structural "color constants" according to an equation of the form $\lambda_x = k_1 k_2 \ldots k_n \lambda_0$. These "color constants," $k_1, k_2, \ldots k_n$, were obtained, for example, as follows: $k_{p\text{-OH}} = \lambda_{\text{aurin}}/\lambda_{\text{benzaurin}} = 0.9657$.



Aurin



Benzaurin

A structural "color constant" was similarly obtained; for instance, that for an oxo link, —O—, was determined from the ratio $\lambda_{\text{fluorescein}}/\lambda_{\text{phenolphthalein}}$, equal to 0.89. In this way, upon choosing *p*-hydroxybenzyl alcohol and two phenol molecules as reference compounds with λ_0 assumed to be 290 mμ and 138 mμ, respectively, and after determining "color constants" for various substituents and structural links, Moir calculated the absorption bands in water solution for a large number of colored substances and obtained values which agreed quite well with the observed ones. In 1923, Steiglitz (284) proposed that within molecules there is an oxidizing–reducing system which, by the process of oxidation and reduction, releases electrons from their intraatomic restraints and starts them vibrating. Dutt (78), in 1926, stated that strain within the molecule from multiple bonds and cyclization causes substances to be colored. Dilthey (74), and later Wizinger (304), implied that "ionoid" compounds are the strongest absorbers of light, although other types of substances may show a weak absorption extending into the visible region. Moir (210), in 1929, made a quantitative study of the triphenylmethane dyes and noted the effect of various auxochromes on both the production of two or three bands and the position of the band of maximum wave length. He concluded that their λ_{max} depends upon the path of the vibrating electrons as influenced by the type and number of auxochromes in the resonating system.

---

[5] For an example of the quantum-mechanical picture see Herzfeld (119).

In an attempt to form a mechanical picture of a conjugated polyene system, Rădulescu (245), in 1931, likened it to a vibrating string which was assembled from many similar units. Each unit has an independent characteristic tension and vibrational frequency but, by vibrating in phase, the units resemble a single oscillator. He discussed the effects of the number of units, and substituents, upon the frequency of vibration of the mutual oscillators.

In 1935, Bury (57) pointed out the important rôle that resonance plays in affecting the color of organic substances. It was about this time that quantitative relationships between absorption spectra and structure based on semiclassical theories began to show promise.[6] Hauser, Kuhn, Smakula, and coworkers (106, 107) measured the spectra of several types of linearly conjugated polyenes and illustrated how the frequency of the lowest-frequency band may be calculated with certain empirical equations, and how the height of this band and the strength of absorption $\left(\int \epsilon d\nu\right)$ (66) vary with the number of conjugated ethylenic groups in the system. In 1936, Clar (67, 76) presented empirical equations by which one can account for the positions of the several bands of condensed-ring hydrocarbons. In 1939 appeared the paper of Lewis and Calvin about which more will be said presently. In 1940, Henrici (115) set up an equation

$$\lambda = 334.2\sqrt{V \cdot s_i}$$

based on classical theories of electrical discharges through gases, to calculate the wave length of the absorption bands of unsaturated compounds. Here, V depends upon the volume of the electron cloud of oscillating p-electrons, which is estimated from interatomic distances, and s_i, the dampening coefficient, is proportional to the dielectric constant and hence the polarizability of the molecule in the direction i. Thus, with increasing number of conjugated unsaturated links the size of the electron cloud will increase and λ_{max} will move toward longer wave lengths. Henrici considered the spectra of condensed-ring hydrocarbons and the diphenylpolyenes. His calculations of λ_{max} for the latter compounds did not agree with the observed values as closely as did those of Hauser, Kuhn, *et al.*

In the past few years many other semiclassical, quantitative treatments of absorption have been given and some of these will be discussed later. From the foregoing brief historical account it can be observed that organic chemists have slowly arrived at the conclusion that the absorption of light is due to vibrating electrons and that a number of qualitative relationships have been molded into a working hypothesis from which, in the later years, there have been formulated a few quantitative generalizations as to the color of organic substances.

Over the past decade quantum-mechanical methods have been applied to the electronic spectra of simple organic molecules and fruitful results have been obtained. The approaches taken by the various workers to determine frequencies and intensities of absorption bands differ essentially in the relative degree of theoretical computation and the extent of substituting empirical data for exact integrals. Using approximate wave functions of the molecular orbital (MO) or of the atomic orbital (AO) type, calculations have been carried out on the spectra of unsaturated molecules whose exact energies, $\int \psi H \psi d\nu$, were determined (91, 96, 122, 277). Except for the time consumed in computing the value of the integrals the method shows considerable promise.

---

[6] A remarkable mathematical attempt for their time to account for molecular spectra was made by Bielecki and Henri in 1913 (24, 112a).

More lucrative have been the methods whereby the theoretically defined integrals are replaced by empirical parameters. The molecular orbital approximation method seems to have advantages over the atomic orbital method in that (*1*) the AO method must assign arbitrary formulations to describe the ground states of "resonating" molecules, while the MO method treats these the same as "normal" molecules, and (*2*) the MO method is usually simpler for the description of excited electronic states. From such information as excitation and ionization potentials, dipole moments, electronegativities, polarizabilities, interatomic distances, bond angles, and force constants, the energy of the ground and first excited states may be evaluated in terms of a single parameter. The value of the parameter is then chosen so as to fit the particular data best. To illustrate the results obtainable by quantum-mechanical methods the wave lengths of the maximum absorption bands for some hydrocarbons are listed in table 1 (91, 196, 277).

TABLE 1

Wave lengths of maximum absorption bands for some hydrocarbons

COMPOUND	λ max (CALCULATED)	λ max (OBSERVED)
Benzene	247	255
Biphenyl	240	252
Naphthalene	295	275
Anthracene	365	370
Naphthacene	450	460
Pentacene	545	580
Phenanthrene	300	295
Pyrene	345	330
Fulvene	365	365
Butadiene	190	210
Azulene	691	700

III. THEORY OF ABSORPTION OF LIGHT[7]

According to current electronic theories ethane and ethylene may have the homopolar electronic arrangements of I and II, or either of the two polar forms, I′ and II′, respectively:[8]

---

[7] For a quantum-mechanical discussion see the articles by the authors listed in footnote number one.

[8] Diradical forms, such as that for ethylene, $\underset{\bullet}{C}H_2—\underset{\bullet}{C}H_2$, are given little consideration, because resonance among forms of different multiplicity is negligible. On the other

$$\begin{array}{ccc} H_3C : CH_3 & H_3C\ :CH_3 & H_3C:\ CH_3 \\ H_3C{-}CH_3 & H_3\overset{+}{C}\ \ \overset{-}{C}H_3 & H_3\overset{-}{C}\ \ \overset{+}{C}H_3 \\ \text{I} & & \text{I}' \\ H_2C{=}CH_2 & H_2\overset{+}{C}{-}\overset{-}{C}H_2 & H_2\overset{-}{C}{-}\overset{+}{C}H_2 \\ \text{II} & & \text{II}' \end{array}$$

When a molecule is placed in an alternating electromagnetic field, such as that of radiations of wave length large compared with the dimensions of the molecule, there is an induced oscillation of electrons throughout the length of the molecule in which the displacement will be proportional to the polarizability of the molecule. It is assumed, as was done by Lewis and Calvin and by Mulliken, that in the electronically excited states as those of I′ and II′ produced by the absorption of light energy, there are oscillations within the molecule of the same character as the induced oscillations mentioned above. The absorption of light causes the transition of the molecule from its ground state to an ionic, electronically excited state and the difference in energy of these two states will determine the frequency of the light absorbed.[9] If it is assumed that the electronic displacements are harmonic oscillations, then the restoring force, according to Hooke's law, will be $-kx$, where x is the electronic displacement from the equilibrium position and k is the restoring force constant. Thus, the energy required for these displacements will be $-\frac{1}{2}kx^2$ and a plot of the potential energy against the electronic displacement will be that of a parabola. The anharmonicity of the less ideal, and more probable, case will be considered later. If the energy is quantized, then the energy levels associated with the successive energy states will be given by $E_v = (v + \frac{1}{2})h\nu_0$; ν_0, the fundamental frequency, is given by $\nu_0 = \frac{1}{2\pi}\sqrt{k/m}$, where m is the effective reduced mass of the vibrating electrons. If E_0 and E_1 are the energies of the ground and first excited states, respectively, then the frequency of the light causing this transition will be

$$E_1 - E_0 = (3/2 - 1/2)h\nu_0 = h\nu_0 \tag{1}$$

and for its wave length,

$$\lambda = C/\nu_0 = 2\pi C/\sqrt{k/m} \tag{2}$$

This means that the chromophoric power of different bonds will vary inversely with their restoring force constants, k. Single bonds with a large k will absorb in the far ultraviolet (152a). Polarization of the second bond of the double bond need not be considered, since it has an extremely large restoring force constant and its absorption would appear in the region where ionization and dissociation take place.

---

hand, if the unpaired electrons have their spins antiparallel, then essentially they form a covalent bond. Furthermore, it is not reasonable that an electric field would cause the electrons to migrate in opposite directions simultaneously.

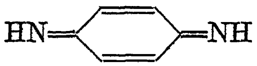
[9] The absorption of light of wave lengths in the region 180–400 mμ corresponds to energy differences of between 70 and 160 kg.-cal./mole, intermediate between those required for the photoionization of single covalent bonds (240, 241) and those required for vibrational or rotational transitions. Energy increments of this magnitude are sufficient to allow the displacement of *mobile electrons* (174) (π or *unsaturation electrons*) of multiple bonds.

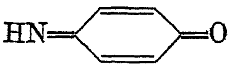
On the basis of the relative chromophoric powers (34) of the various double bonds, the order of decreasing k must be:

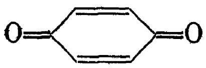
	$H_2C{=}CH_2$	$(CH_3)_2C{=}NCH_3$	$(CH_3)_2C{=}O$
λ_{max} =	200 mμ	230 mμ	280 mμ
	$CH_3N{=}NCH_3$	$(CH_3)_2C{=}S$	$C_4H_9N{=}O$
λ_{max} =	347 mμ	400 mμ	665 mμ

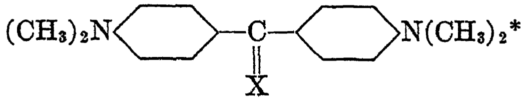
Simple compounds containing these bonds exhibit a maximum wave-length absorption band, λ_{max}, approximately as indicated. Additional examples are the following compounds with their approximate absorption maxima:

$CH_2{=}CHCH{=}CH_2$	$CH_2{=}CHCH{=}O$	$O{=}CHCH{=}O$
220 mμ	350 mμ	460 mμ (198)


colorless (302)

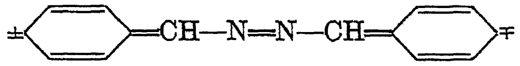

pale yellow


deep yellow



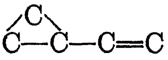
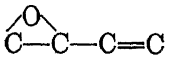
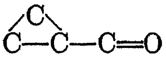
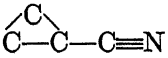
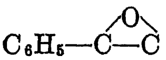
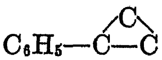
*λ_{max} increases in the order given, where X is CH_2, NH, O, S (54).

The order of increasing chromophoric power for these double bonds is due to the increased strain within the bonds (151). With increasing strain there results a less stable ground state, causing a smaller difference in the potential energies of the ground and first excited states, and hence an absorption of light (excitation) of longer wave lengths. An interesting corollary was noted by Lewis and Calvin (182). They pointed out that although benzalazine, $C_6H_5CH{=}NN{=}CHC_6H_5$, contains two stronger chromophores ($C{=}N > C{=}C$) than 1,4-diphenylbutadiene, $C_6H_5CH{=}CHCH{=}CHC_6H_5$, the former compound ($\lambda_{max}$ = 265 mμ) absorbs light at shorter wave lengths than does the latter (λ_{max} = 334 mμ). In the predominant form of the excited state of benzalazine,



there is an N=N bond and because of this highly strained bond there is a resistance to the complete conjugation throughout the molecule, that is, a less stable excited state. This increases the energy required for excitation to the extent that the maximum absorption band for the azine occurs at shorter wave lengths. Ferguson and Goodwin (86) found this to be true in a number of cases containing the C=N—N=C and the —N=C—C=N— structural systems.

The cyclopropyl group may be considered a chromophore but weaker than an ethylenic bond, since in cyclopropane the bonds are under less strain. This viewpoint (15, 63, 78, 193) is supported by the fact that the color deepens in going from cyclohexane to cyclopropane and also for the series cyclohexanone, cyclopentanone, cyclobutanone, and ketene (20, 89, 93). In this connection a number of studies (61, 109, 155, 200a, 257a) have shown that the cyclopropyl ring and the epoxy group have chromophoric powers approaching that of an ethylenic bond. When these two small saturated groups are adjacent to an ethylenic bond or a carbonyl bond the resulting systems are found to have absorption maxima in between those of a monoene, or carbonyl compound, and a diene, or an α,β-unsaturated carbonyl system. This is illustrated below, where the λ_{max} for skeleton structures are indicated.

$C{=}C$ 175 $m\mu$	$C{=}C{-}C{=}C$ 217 $m\mu$	 >175 $m\mu$	 <210 $m\mu$
$C{=}O$ 280 $m\mu$	$C{=}C{-}C{=}O$ 310–330 $m\mu$	 290 $m\mu$ (273)	
$C{\equiv}N$ 180 $m\mu$	$C{=}C{-}C{\equiv}N$ 214–217 $m\mu$	 210 $m\mu$	
$C_6H_5{-}R$ 259 $m\mu$	$C_6H_5{-}C{=}C$ 290 $m\mu$	 260 $m\mu$	 274 $m\mu$

In line with the above concept, acetylene is found to absorb at longer wave lengths than ethylene (283). On the other hand, when it is conjugated with other unsaturated bonds it closely resembles the ethylenic bond spectrographically. This is perhaps due to the increased strain in the excited molecule, where one carbon atom forms two double bonds,

$$R{-}C{\equiv}C{-}CH{=}CHR \qquad R{-}\overset{\pm}{C}{=}C{=}CH{-}\overset{\mp}{C}HR$$

counterbalancing the greater strain in the ground state of the triple bond over that of the double bond. For instance, cumulated double bonds, $C{=}C{=}C$, $C{=}C{=}O$, $N{=}C{=}N$, etc., are found to absorb light at longer wave lengths than when these bonds are conjugated, owing to a less stable ground state and hence a smaller difference between the energies of the ground and excited states (56, 64, 173). The resemblance between the spectra of vinylacetylenes and those of α,β-dienes was pointed out and illustrated by Heilbron, Jones, and coworkers (108).

Since auxochromes, like chromophores, are found to exhibit high-intensity absorption in the far ultraviolet and the conjugation of two auxochromes produces bathochromic as well as hyperchromic effects, and since saturated groups like the cyclopropyl and epoxy groups are found to be spectroscopically similar to double bonds, Braude (34) suggests a redefinition of the classical terms *chromophore* and *auxochrome* to "covalently unsaturated" and "covalently saturated" groups, respectively. For instance, it is found that the introduction of an amino group, long recognized as one of the principal auxochromes, at the terminal carbon atom of a conjugated system causes a greater bathochromic effect than the addition of another ethylenic or other unsaturated group (25; see also reference 300, page 1986).

There are two points concerning spectra about which little will be said: (*1*) the effect of the solvent; (*2*) the intensity of absorption bands. It is commonly known that the shape and position of the peaks of absorption bands greatly depend upon the solvent. Several authors (46, 66, 159, 171, 191, 244, 265, 270) have attempted to determine the way in which the solvent influences the spectrum and causes a deviation from the Beer–Lambert law. Shepard and his coworkers (274) have found a number of trends in the effect of the solvent with such properties of the solvent as its dielectric constant, its dispersion or index of refraction, and with the type of solvent, whether it is polar or non-polar, acidic or basic, aromatic or aliphatic, or is an associating solvent, but no one of these correlations has been rigid. There is little doubt that the effects are caused through aggregation between solvent and solute or solute and solute molecules, and also dissociations and associations (28, 32, 79, 103, 154, 169, 170, 180, 183, 187, 216, 291); nevertheless, regardless of the several theories proposed (127, 207, 265, 274, 280), a general fundamental explanation is still lacking.

According to classical electromagnetic theory (35) and quantum mechanics it seems reasonable to say that the intensity of absorption bands depends partly upon the probability of the transition from the ground to the ionically excited states of the molecule (31, 34, 220), upon the polarity of the excited states, and upon the magnitude of the electronic displacements involved in passing from the normal to the excited states (238). The transition probability is calculable for certain simple substances by quantum mechanics, but experimentally the organic chemist has learned little to help him predict the band intensities. Theoretical considerations lead to the conclusion that small absorption coefficients of the order of that of benzene usually indicate "forbidden" transitions (281). Strong absorption occurs only when there is a large electric moment connected with the transition. It can be shown for symmetrical molecules, such as benzene and mesitylene, that when an unsymmetric vibration is singly excited with the electronic transition, a small transition moment is produced and the spectrum will appear with weak intensity. That is, instead of a 0–0 band (electronic transition without vibration) as in allowed transitions, there will be a 0–1 band which corresponds to a transition from the vibrationless ground state to the upper state in which that particular vibration is excited with one quantum. Thus, Sponer (281) found in the long-wave region of the spectrum of 1,3,5-trichlorobenzene small absorption coefficients like those of benzene. On the other hand, the unsymmetrical isomer, 1,2,4-trichlorobenzene, shows moderately strong absorption in the same region.

Several correlations have been found (34, 38, 40, 70, 119, 230, 243, 290) concerning the effect upon λ_{max} of substituents in the aromatic nucleus but fundamental generalizations (34, 43, 68, 90, 101, 102, 118, 133, 238, 288) are limited in scope. Very recently Doub and Vandenbelt (76a) made an excellent study of the ultraviolet absorption spectra of mono- and di-substituted benzenes, from which a remarkable systemization was possible. Doub and Vandenbelt have considered absorption to be primary when the molar extinction coefficient, ϵ, is equal to or greater than 6×10^3, while secondary absorption results in ϵ being less than 2.6×10^3, usually much less. Thus, the absorption band of benzene near 200 mμ ($\epsilon_{max} = 7400$) is the first primary band, and the long-wave band near 250 mμ ($\epsilon_{max} \sim 200$) is the first secondary band. From their work it appears that greater success will be achieved in understanding the absorption of aromatic compounds by focusing attention on the primary bands rather than on the low-intensity secondary band.

When the substituent groups were divided into electron-donating (ortho and para directing) and electron-attracting (meta directing) types, and arranged in order of increasing $\Delta\lambda$ (displacement of the primary band relative to the 203.5 mμ band of benzene) values, the following series was obtained by Doub and Vandenbelt:

ortho and para directing

$$CH_3 < Cl < Br < OH < OCH_3 < NH_2 < O^-$$

meta directing

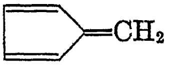
$$NH_3 < SO_2NH_2 < COO^- = CN < COOH < COCH_3 < CHO < NO_2$$

In both series, the largest bathochromic shift is with the groups which exhibit the greatest amount of electronic interaction (mesomerism or resonance rather than coulombic force) with the ring. In the case of the disubstituted compounds, when the two substituents are of the same type the red shift is close to the displacement that is the larger for the two groups, and when the two substituents are of different types, and ortho or para situated, the bathochromic shift is much larger than the combined displacements from the single groups.

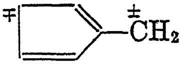
IV. RESONANCE AND COLOR

According to equation 1, the smaller the difference in energies of the ground and excited states the lower is the frequency, or the longer is the wave length, of the light absorbed. One can only predict the effects of resonance and other influences by considering separately the energy changes brought about in the ground and excited states (240, 294). It is not the magnitude of the resonance energy of a substance which determines λ_{max} (199, 299) but whether the resonance stabilizes the excited states more than the ground state (256).

The relationship between color and resonance can be clearly disclosed by regarding the fact that benzene and naphthalene are colorless, while their isomers, fulvene (299) and azulene (237, 292), are yellow and blue, respectively. According to well-founded resonance theories, structures involving a separation of charge contribute chiefly to excited states. The Kekulé and Dewar resonance of benzene and naphthalene accounts for most of their resonance energies, while the chief resonating forms of fulvene and azulene are of the polar types IIIa and IVa.[10]

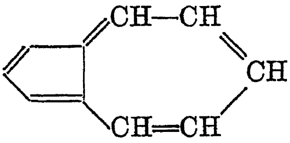


III

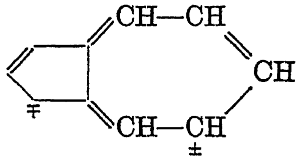


IIIa

Fulvene



IV

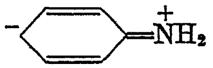


IVa

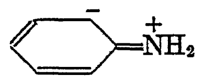
Azulene

Although benzene and naphthalene have large resonance energies the resonance is predominantly between forms that stabilize the ground state, increasing the difference in energy between the ground and first excited states, such that they absorb below 300 mμ. On the other hand, the resonance of fulvene and azulene lowers the potential energy of the first excited states with respect to the ground state to the extent that their absorption occurs in the visible. For the same reason, cycloöctatetraene, whose resonance energy is less than that of benzene, absorbs at longer wave lengths than benzene (200).

It is apparent that, in general, the color of a molecule will be deeper the greater is the resonance among ionic forms or forms involving a separation of charge.[11] Many authors have shown that λ_{max} is larger for compounds exhibiting the greatest amount of resonance but, in general, such resonance has involved polar structures (57, 125, 126, 269, 273, 290). For instance, the values of λ_{max} for aromatic amines are greater than those of the corresponding compounds without the amino group, owing to the resonance among such ionic forms as



and



while in acid solution such resonance is inhibited and the spectra revert to those of the parent compounds (72, 112, 136, 170, 289, 305). The resonance of enols, phenols, and naphthols is less than that of their ions and, accordingly, a bathochromic shift occurs in passing from neutral to basic solutions (28, 84, 173a). Schwarzenbach and coworkers (271) have correlated the color of phthalein-type indicators with the symmetry of the ions present at various pH values and have pointed out that the greater the equivalence in resonating forms the deeper is the color of the ion.

---

[10] The non-coplanarity of azulene decreases the contribution from the two equivalent forms of type IV, while there are a number of forms of type IVa.

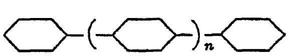
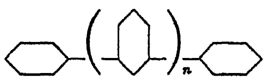
[11] Mulliken (219) and others have stated from wave-mechanical considerations that absorption of light takes place predominantly through transitions to charge-resonance structures.

V. CONJUGATION AND INSULATION OF CHROMOPHORES

It was very early recognized that the longer the conjugation within a molecule the deeper will be its color (73, 123). The effect of conjugation, or of insulation, of chromophores is strikingly revealed by observing the spectra of two compounds one of which has two chromophoric systems conjugated, while the other has the same two chromophoric systems separated by one or more saturated carbon atoms[12] (250) or meta-oriented about a benzene ring. For instance, the spectrum of 1,5-hexadiene, $CH_2{=}CH{-}CH_2{-}CH_2{-}CH{=}CH_2$, is identical with that of 1-pentene except for a twofold intensity, while 1,3-pentadiene has a larger λ_{max} by about 20 mμ (64). Then too, although the rubber hydrocarbon molecule contains thousands of unconjugated carbon–carbon double bonds, its λ_{max} is near that of ethylene (267).

TABLE 2

Wave lengths of the maximum absorption bands of the meta and para "polyphenyls" (97)

<table>
<tr><th colspan="2">PARA
</th><th colspan="2">META
</th></tr>
<tr><th>n</th><th>λ max</th><th>n</th><th>λmax</th></tr>
<tr><td></td><td>mμ</td><td></td><td>mμ</td></tr>
<tr><td>0</td><td>251.5</td><td>0</td><td>251.5</td></tr>
<tr><td>1</td><td>280</td><td>1</td><td>251.5</td></tr>
<tr><td>2</td><td>300</td><td>7–12</td><td>253</td></tr>
<tr><td>3</td><td>310</td><td>13</td><td>254</td></tr>
<tr><td>4</td><td>317.5</td><td>14</td><td>255</td></tr>
</table>

Numerous examples of this conjugation and insulation effect are reported in the literature (18, 94). To mention a few:

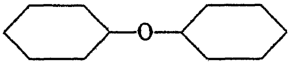
(*1*) The absorption of propenylbenzene, $C_6H_5CH{=}CHCH_3$, extends to longer wave lengths by 20 to 30 mμ beyond that of the corresponding allylbenzene, $C_6H_5CH_2CH{=}CH_2$, and with much greater intensity; the allyl group has the same auxochromic effect as a saturated side chain (61, 73, 124, 141, 214, 231, 248, 249).

(*2*) *Insulation:* The following compounds all have λ_{max} at 262 mμ (97, 192, 251):

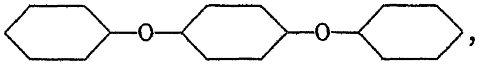
$C_6H_5CH_2CH_2C_6H_5$ $(C_6H_5)_2CH_2$ $(C_6H_5)_3CH$ $(C_6H_5)_4C$

---

[12] Not necessarily saturated carbon atoms for, regardless of the oxonium properties of the oxygen atoms, the compounds

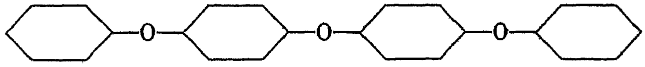


,



,

and



all have similar spectra (203; see also reference 130).

TABLE 3

Wave lengths of the maximum absorption bands of some similarly conjugated or insulated chromophoric systems

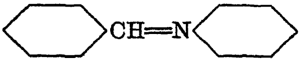
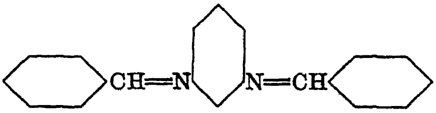
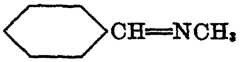
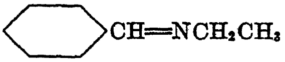
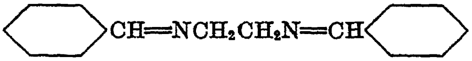
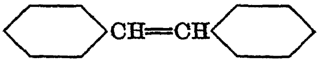
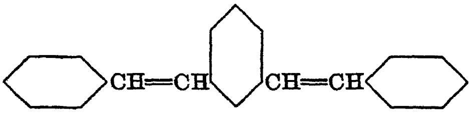
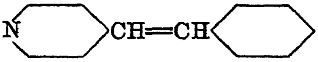
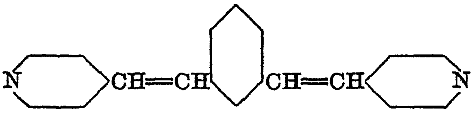
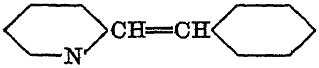
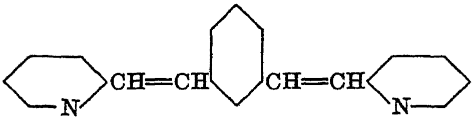
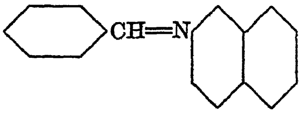
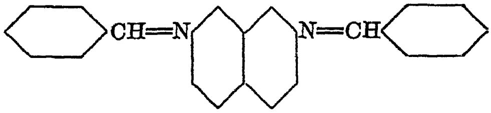
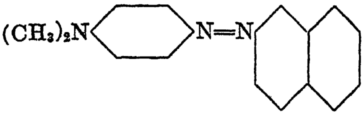
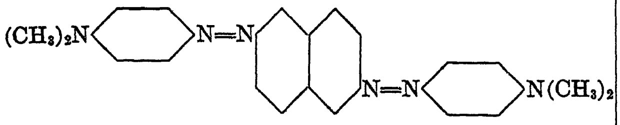
COMPOUND	λ_{max}	ϵ_{max}	REFERENCES
	mμ		
	263	16,800	(85)
	267	33,800	(85)
	247	17,200	(85)
	245	15,900	(85)
	247	29,800	(85)
	295	26,300	(26, 87)
	298	53,700	(26)
	307	29,700	(26)
	308	46,800	(26)
	310	27,600	(26)
	314	50,100	(26)
	323	10,000	(117)
	313	22,000	(117)

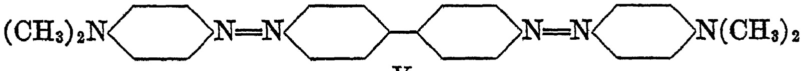
TABLE 3—*Concluded*

COMPOUND	λ max	ε max	REFERENCES
	mμ		
	422	36,000	(117)
	450	73,400	(117)
$CH_3(CH{=}CH)_2CHOHC{\equiv}CH$	230	28,500	(110)
$CH_3(CH{=}CH)_2CHOHC{\equiv}CCHOH(CH{=}CH)_2CH_3$	229	74,000	(110)
$CH_3(CH{=}CH)_3CHOHC{\equiv}CH$	267.5 278	55,000 44,500	(110)
$CH_3(CH{=}CH)_3CHOHC{\equiv}CCHOH(CH{=}CH)_3CH_3$	269 281	100,000 81,000	(110)

(*3*) Consider the para and the meta "polyphenyls" reported by Gillam and Hey (97), which are listed in table 2. For the para series, in which there is conjugation throughout the molecules, λ_{max} increases with increasing length of the molecules, while in the meta series where, starting with biphenyl, each additional phenyl ring is placed meta to the rest of the chain, the conjugation extends only through any two adjacent rings and is thus of the same lengths as in biphenyl. For as many as sixteen phenyl rings so attached, λ_{max} is practically the same as for biphenyl.

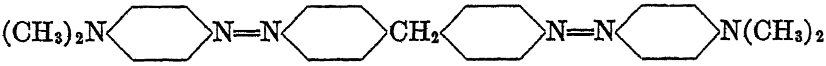
(*4*) Molecules with two insulated chromophoric systems will absorb light of near the same wave length as a molecule containing only one such chromophoric system, but the intensity of the light absorbed by the former molecule will be approximately twice that of the latter. This is brought out in table 3.

This phenomenon can further be observed in figure 1 for monoazo and biszao dyes, as measured by Piper and Brode (236; see also 41). Here is plotted the intensity for the bisazo dyes,



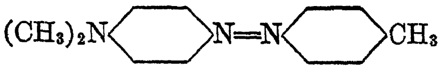
V

and



VI

and twice the intensity for the monoazo dye:



VII

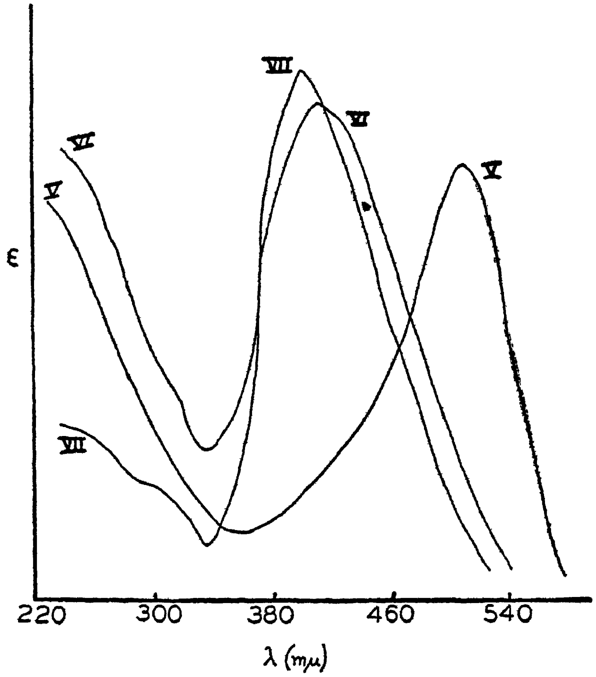
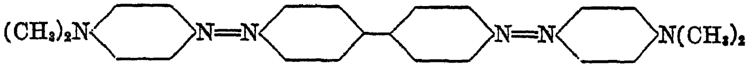
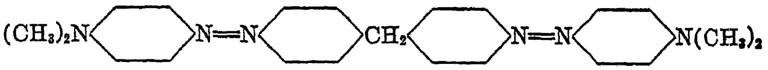


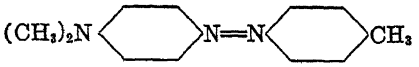
Fig. 1. Absorption spectra of V and VI and 2 × ε for VII, measured by Piper and Brode (236).



V



VI



VII

It can be seen that twice the molar absorption for the monoazo dye VII corresponds well to that of the insulated bisazo dye VI, but the conjugated bisazo dye V shows a new band at longer wave lengths.

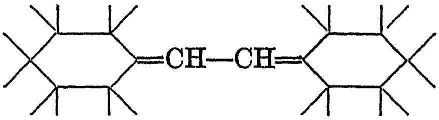
To cite another excellent example, the curve for 2 × ε for acetone is identical with the curve of ε for 3,6-diketoöctane, $C_2H_5COCH_2CH_2COC_2H_5$, while biacetyl, $CH_3COCOCH_3$, has a much larger λ_{max} (249).

These examples serve to illustrate how λ_{max} is greatly affected by the conjugation or insulation of the chromophoric systems. This fact is often used to decide upon the structure of compounds (167, 227) for which there is a question as to the location of certain double bonds.

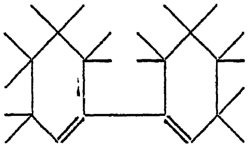
VI. SPECTRA OF COMPOUNDS CONTAINING TWO CONJUGATED CHROMOPHORES

A. Dienes

Many authors (8, 30, 68, 90, 209, 229) have observed the increase in λ_{max} upon replacing a hydrogen atom by an alkyl group on a carbon–carbon double bond. Mulliken (218, 222; see also 155) has attributed this to hyperconjugation, that is, a coupling between the σ-electrons of the adjacent C—H bonds of an alkyl group with the bonding electrons of the C—C$_{alkyl}$ linkage (compare the conclusions of Price and Walsh (241) and of Bateman and Koch (17, 18)). Furthermore, the bathochromic shift is approximately the same for all substituents attached by a saturated carbon atom. Upon inspection of substituted α,β-dienes Woodward (306) noticed that substitution apparently is not the sole factor affecting λ_{max}. For example,

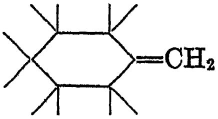


has a λ_{max} of 247 mμ while both

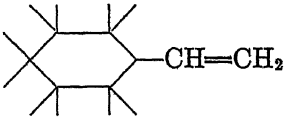


and $(CH_3)_2C{=}CHCH{=}C(CH_3)_2$

have λ_{max} at 237 mμ, i.e., 10 mμ lower. It is known from heats of hydrogenation (169) that a double bond exocyclic to a six-membered ring,



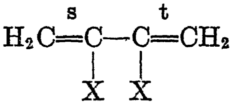
is under greater strain than an endocyclic double bond:



Also it was pointed out above that strain within a molecule will cause it to absorb at longer wave lengths. These two facts led Woodward to the conclusion that a diene with exocyclic double bonds will have a λ_{max} greater than that anticipated from the number of substitutions on the system.

On this basis Woodward started with the λ_{max} for 1,3-butadiene and, for each substitution and for each exocyclic double bond, assumed a bathochromic shift of 5 mμ. With these three constants he calculated the λ_{max} for eleven symmetrically substituted α,β-dienes with an average deviation of 1 mμ from the observed values.

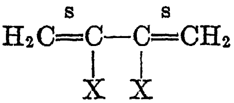
Woodward gave a somewhat different treatment to unsymmetrical α,β-dienes, but one that will hold as well for the symmetrical dienes. Consider an unsymmetrical α,β-diene (X) with double bonds designated as s and t:



$$H_2C\overset{s}{=}\underset{\overset{|}{X}}{C}-\underset{\overset{|}{X}}{C}\overset{t}{=}CH_2$$

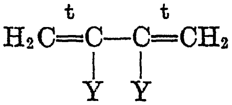
X

X may be thought of as a composite of two symmetrical α,β-dienes, VIII and IX.



$$H_2C\overset{s}{=}\underset{\overset{|}{X}}{C}-\underset{\overset{|}{X}}{C}\overset{s}{=}CH_2$$

VIII



$$H_2C\overset{t}{=}\underset{\overset{|}{Y}}{C}-\underset{\overset{|}{Y}}{C}\overset{t}{=}CH_2$$

IX

It would be reasonable to expect λ_{max} for X to be the mean of the values of λ_{max} for the two related dienes, VIII and IX. That is,

$$\lambda_{st} = \frac{\lambda_{ss} + \lambda_{tt}}{2}$$

where λ_{st}, λ_{ss}, and λ_{tt} are the calculated wave lengths for the maximum absorption bands of the unsymmetrical and symmetrical α,β-dienes, respectively. In this manner Woodward calculated λ_{max} for several unsymmetrical α,β-dienes, again assuming that each exocyclic double bond causes a 5-mμ bathochromic shift in λ_{max}. Several examples are taken from Woodward's table and listed in table 4. Woodward's calculations for eighteen compounds have an average deviation of 3.5 mμ from the observed values.

It is possible, then, to calculate with reasonable accuracy the position of the maximum absorption band for α,β-dienes containing no other chromophores and having the two double bonds not within the same ring (21).

B. α,β-Unsaturated carbonyl compounds

It was early noted (23, 206, 262) that α,β-unsaturated ketones have characteristic spectra. An isolated carbonyl group gives a low-intensity band ($\epsilon = 10$–100) near 275 mμ, while an ethylenic group gives a high-intensity band ($\epsilon \simeq 10^4$) near 195 mμ. When these two groups are conjugated, producing an α,β-unsaturated carbonyl compound, the two bands, referred to as *K* and *R* bands following Burawoy's (54) terminology, occur at longer wave lengths (81).

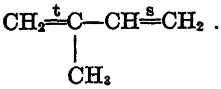
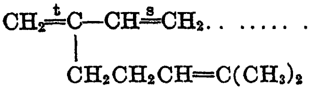
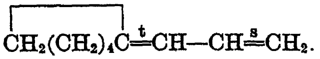
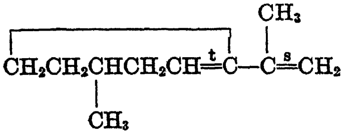
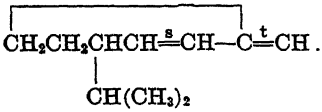
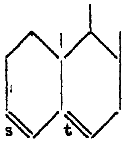
K band..................................	220–260 mμ	$\epsilon = 10^4$
R band..................................	310–330 mμ	$\epsilon < 100$

Since the *R* band is of such low intensity, most attention is focused upon the *K* band.

After studying a number of α,β-unsaturated carbonyl compounds, Woodward (307) found that the values of λ_{max} for such compounds can be approximated in fair agreement with the observed values if one assumes that a carbon-attached substituent on the conjugated system causes a bathochromic shift of 10–11 mμ and an exocyclic double bond causes a shift of 5 mμ. His table of values of λ_{max} to be expected on this basis for mono-, di-, and tri-substituted α,β-unsaturated ketones is as follows:

TABLE 4

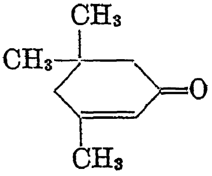
Woodward's (306) calculated and observed values of λ_{max} for some unsymmetrical α,β-dienes

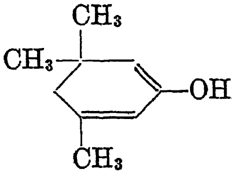
COMPOUND	λ_{ss}	λ_{tt}	$\frac{\lambda_{ss} + \lambda_{tt}}{2}$	$\lambda_{obsd.}$
	mμ	*mμ*	*mμ*	*mμ*
$CH_3CH\overset{t}{=}CHCH\overset{s}{=}CH_2$	217	227	222	223.5
 $CH_2\overset{t}{=}C(CH_3)—CH\overset{s}{=}CH_2$	217	227	222	220
 $CH_2\overset{t}{=}C(CH_2CH_2CH=C(CH_3)_2)—CH\overset{s}{=}CH_2$	217	227	222	224.5
 $CH_2(CH_2)_4C\overset{t}{=}CH—CH\overset{s}{=}CH_2$	217	247	232	236.5
 $CH_2CH_2CH(CH_3)CH_2CH\overset{t}{=}C—C(CH_3)\overset{s}{=}CH_2$	227	237	232	235
 $CH_2CH_2CH(CH(CH_3)_2)CH\overset{s}{=}CH—C\overset{t}{=}CH$	227	237	232	232
$\Delta^{3,5}$-Cholestadiene . 	237	247	237	235

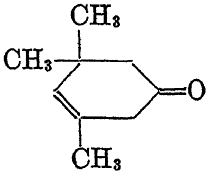
SUBSTITUTION		λ_{max} TO BE EXPECTED
		mμ
α or β		225
α,β or β,β	no exocyclic bond	235
	one exocyclic bond	240
α,β,β	no exocyclic bond	247
	one exocyclic bond	252

Evans and Gillam (81, 82, 98) and other investigators (14, 93, 300) have measured the spectra of many α,β-unsaturated ketones and aldehydes and found additional evidence to substantiate Woodward's table. However, Evans and Gillam found that the aldehydes have a λ_{max} only 5 mμ lower than that of the corresponding ketones, rather than 10 mμ. In this connection, Evans and Gillam (83) measured the spectra of dienones and dienals, C=C—C=C—C=O, to find that their λ_{max} fall between 269 and 317 mμ; here too they found that a substitution causes roughly a 10-mμ shift zmd that the aldehydes absorb light of 5 mμ shorter wave length than the corresponding ketones. Also, they found that there is a slightly larger substitution effect the farther away is the substitution from the carbonyl carbon atom. Wilds *et al.* (300) find that a phenyl group exerts approximately the same bathochromic effect on the λ_{max} of α,β-unsaturated ketones as does a second double bond.

Klotz (153) has pointed out an excellent illustration of how these generalizations about the position of the wave length of the maximum absorption band may be of use. In the reaction of isophorone (XI) with methylmagnesium bromide, Kharasch and Tawney (149) could not decide from chemical tests whether the structure of the product was XII or XIII.


XI


XII


XIII

If it were XII, it should have a λ_{max} just a little larger than that of 1,3-hexadiene, while if it were XIII it should have a spectrum characteristic of a saturated ketone, i.e., $\lambda_{max} \backsim 275$ mμ, $\epsilon < 100$. Kharasch and Tawney (150) recorded the spectra of isophorone and of the product; from figure 2 one can easily decide that the latter has the structure of XIII and is $\Delta^{3,4}$-3,5,5-trimethylhexenone Notice, too, that isophorone has the spectrum of an α,β-unsaturated ketone·

C. α,β-Unsaturated imino compounds

Evans and Gillam (82) chose the semicarbazones of α,β-unsaturated carbonyl compounds, $RCH{=}CHCH{=}NCONH_2$, as the simplest class of compounds containing the C=C—C=N system. For these compounds they noted four effects (typical spectra are drawn in figure 3): (*1*) a bathochromic and hyperchromic effect in the maximum absorption band over the corresponding carbonyl compound; (*2*) a disappearance of the α,β-unsaturated carbonyl *R* band; (*3*) a loss in difference between the aldehyde and ketone derivatives; (*4*) the lack of a regular substitution effect and the fact that all the of λ_{max} fall within the range 267 ± 7.5 mμ (53, 100, 118, 152). The authors turned to the oximes of α,β-unsaturated carbonyl compounds, but again could not detect a regular substitution effect on the C=C—C=N system.

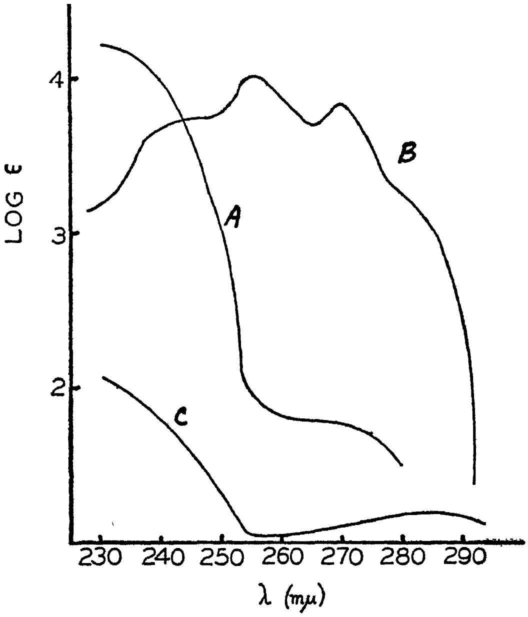


FIG. 2. Absorption spectra of isophorone (XI) (A); 1,3-cyclohexadiene (B); $\Delta^{3,4}$-3,5,5-trimethylhexenone (XIII) (C). Redrawn from reference 153 through the courtesy of the Editor, Professor Norris W. Rakestraw.

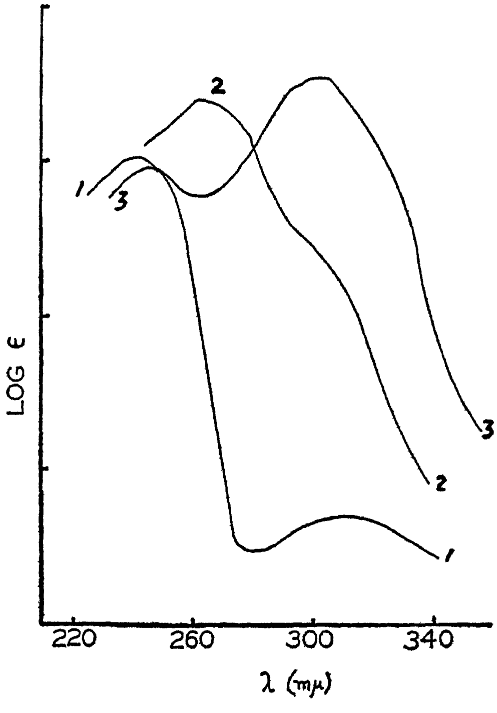
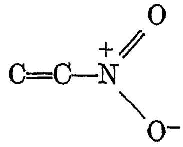


FIG. 3. Absorption spectra of a typical α,β-unsaturated carbonyl compound (curve 1), an α,β-unsaturated carbonyl semicarbazone (curve 2), and an α,β-unsaturated carbonyl thiosemicarbazone (curve 3).

Upon studying the thiosemicarbazones, $RCH{=}CHCH{=}NCSNH_2$, Evans and Gillam found that all of them have two bands; one in the region of 245 mμ and one in the small range of 301.5 ± 2 mμ. Nevertheless, an orderly substitutive effect was not observed. Since the thiosemicarbazones of saturated carbonyl compounds have their two bands near 230 mμ and 271 mμ, the authors point out that the thiosemicarbazones offer another means of spectroscopic detection of isolated and α,β-unsaturated carbonyl compounds. That is, the absorption bands for the saturated and unsaturated compounds fall in different regions (109).

	SATURATED	α,β-UNSATURATED
	mμ	mμ
Carbonyl	275 ($\epsilon < 100$)	220–250 ($\epsilon \backsim 10^4$)
Thiosemicarbazones	230 and 271	245 and 301.5

D. Nitroölefins

Braude, Jones, and Rose (37) found that although an isolated nitro group gives rise to a low-intensity band near 270 mμ (34), the  $C{=}C{-}\overset{+}{N}\genfrac{}{}{0pt}{}{\nearrow O}{\searrow O^-}$ system exhibits a high-intensity band at 225 mμ but none at longer wave lengths as do the α,β-unsaturated carbonyl compounds. Lengthening of the conjugated chain as in α-nitrobutadiene and β-nitrostyrene, i.e., $CH_2{=}CHCH{=}CHNO_2$ and $C_6H_5CH{=}CHNO_2$, respectively, results in a high-intensity band appearing near 300 mμ. In addition, the shorter wave-length band near 225 mμ persists, which is peculiar to the nitro compounds. Substituents attached to the α,β-ethylenic bond of the nitroölefins cause auxochromic effects; thus $\Delta\lambda_{\text{alkyl}} =$ *ca.* 10 mμ and $\Delta\lambda_{\text{Br}} =$ *ca.* 30 mμ.

VII. LINEARLY CONJUGATED SYSTEMS

It was shown above how $\lambda_{\max}$ is affected by the conjugation of chromophores and, in general, $\lambda_{\max}$ is larger the longer is the conjugated system. One may consider molecules containing many chromophores conjugated in a linear fashion such that the molecule has essentially only one axis. There are several types of such linearly conjugated systems, among which may be included the following (possible resonating forms are indicated):

1. Polyenes (163):

$$R(CH{=}CH)_nCH{=}CHR,\ R\overset{\pm}{C}H(CH{=}CH)_n\overset{\mp}{C}HR$$

Examples: diphenylpolyenes (71, 107), carotenoids (165, 309), dialkylpolyenes (166), and dyes of the malachite green type in strong acid

2. *Polyenals and polyenimines:*

$R(CH{=}CH)_nCH{=}O$, $R\overset{+}{C}H(CH{=}CH)_n\overset{-}{O}$

Examples: polyenaldehydes

$R(CH{=}CH)_nCH{=}NR$, $R\overset{+}{C}H(CH{=}CH)_n\overset{-}{N}R$

Examples: polyenal Schiff bases (anils (118), phenylhydrazones (36), etc.)

$R(CH{=}CH)_n\,CH{=}NN{=}CH(CH{=}CH)_mR$,

$$\left\{\begin{array}{l} R\overset{+}{C}H(CH{=}CH)_n\overset{-}{N}N{=}CH(CH{=}CH)_mR \\ R\overset{-}{C}H(CH{=}CH)_nN{=}\overset{+}{N}{=}CH(CH{=}CH)_mR \\ R\overset{\pm}{C}H(CH{=}CH)_mN{=}N(CH{=}CH)_m\overset{\mp}{C}HR \end{array}\right\}$$

Examples: polyene-azines (85)

3. *Amide type* (simplest member is an amide)

$R_2N(CH{=}CH)_nCH{=}O$, $R_2\overset{+}{N}{=}CH(CH{=}CH)_n\overset{-}{O}$

Examples: merocyanines (46, 55)

4. *Amidinium type*

$R_2N(CH{=}CH)_nCH{=}\overset{+}{N}R_2$, $R_2\overset{+}{N}{=}CH(CH{=}CH)_nNR_2$

Examples: polyene-azomethines (44, 55, 156) and dyes of the malachite green type (197)

5. *Carboxyl ion type* (simplest member is the ion of formic acid)

$^{-}O(CH{=}CH)_nCH{=}O$, $O{=}CH(CH{=}CH)_nO^{-}$

Examples: polyenedicarboxylic acids and esters (16, 285)

These five types of dyes fall into two classes:[13]

Class I: Dyes to be included in this class are those for which there is one predominant canonical structure, such as is found for those of types 1, 2, and 3, above. These compounds give rise to ionic resonating forms of higher potential energy than the normal classical structures.

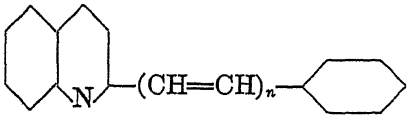
According to equation 2 the wave length of light absorbed by a unit vibrating chromophore can be given by the equation $\lambda = 2\pi C/\sqrt{k/m}$. If n such chromophores are joined, each with the same restoring force constant, k, and effective mass of vibrating electrons, m, and if they vibrate in phase such that the system resembles a single oscillator, one can express the wave length of the absorbed light by a similar equation, $\lambda = 2\pi C/\sqrt{k/nm}$. By squaring both sides,

$$\lambda^2 = \frac{4\pi^2 C^2 m}{k} \cdot n$$

---

[13] See a similar classification by Schwarzenback, Lutz, and Felder (272).

one gets an equation for a straight line, $\lambda^2 = A + Bn$, where B is a constant, equal to $4\pi^2 C^2 m/k$, and A is the intercept value when n is zero. Therefore, the square of the wave length of the maximum absorption band, $\lambda^2_{\max}$, should vary linearly with the number of chromophores.[14] Lewis and Calvin (182) showed that this equation holds true for the diphenylpolyenes, $C_6H_5(CH{=}CH)_nC_6H_5$, whose spectra were measured by Hauser, Kuhn, and coworkers (107). Compton and Bergmann (71) found this same relationship to hold for the α-(α-quinolyl)-ω-phenylpolyenes:



The latter authors point out the very close similarity between the spectra of the n^{th} member of this series and that of the $(n + 1)^{\text{th}}$ member of the diphenylpolyene series, giving evidence that the chromophoric character of the α-quinolyl group is equivalent to that of a styryl group.

From the measurements recorded by Hauser, Kuhn, *et al.* (106, 107) for the polyenals, and their own for the polyenimines, Ferguson and Branch (85) illustrated that, although there are different types of chromophores (C=O, C=C, C=N) in the conjugated chains of dyes of types 2 and 3, above, there still exists essentially the same type of oscillator, in that $\lambda^2_{\max}$ varies linearly with the number of chromophores, n. A plot of λ^2 *vs.* n for these compounds, and also for the diphenylpolyenes, is shown in figures 4a and 4b.

Measurements with the simple polyenes, $R(CH{=}CH)_nR$, are not completely satisfactory, in that the few known values of $\lambda_{\max}$ were determined in different solvents and, too, close agreement between values reported by different authors is lacking. However, a plot of $\lambda^2_{\max}$ against the chain length approximates a straight line. It is of interest to notice, as Heilbron, Jones, and their collaborators have pointed out (108), that the conjugated polyenyne molecules closely resemble the polyenes spectroscopically. For example, from the value of $\lambda_{\max}$ for butadiene (217 mμ) and an assumed value for hexatriene, 265 mμ, a straight line can be drawn whose equation, $\lambda^2 = (0.09 + 2.31n) \times 10^4$ mμ, can be used to calculate the $\lambda_{\max}$ for longer molecules, both polyenes and polyenynes. This has been done and the calculated values are compared with observed values in table 5. Little significance should be attached to these calculated values since solvent effects, which may cause changes in $\lambda_{\max}$ by 20 mμ, and substitution effects have not been considered.

The results are interesting when one groups the conjugated polyene and polyenyne series together and calculates $\lambda_{\max}$ by making substitution corrections as Jones did for the α,β-dienes. Here, values of $\lambda_{\max}$ (calculated) were obtained for the dienes by adding, to the $\lambda_{\max}$ of butadiene, 5 mμ for each alkyl and 6 mμ for each RCHOH— substituent, and for the vinylacetylenes, 6 mμ for each

---

[14] Several investigators have expressed this same relationship by similar equations (4, 5, 114, 165).

RCHOH— and 1 mμ for each alkyl substituent. In the case of the $n = 3$ compounds, the base value for a triene was taken as 265 mμ, for a C═C—C═C—C≡C system as 259 mμ, and for a C═C—C≡C—C═C system as 253 mμ. With the trienes, 6 mμ for each RCHOH— and 5 mμ for each alkyl substituent was added to the base value, and for both of the other two systems

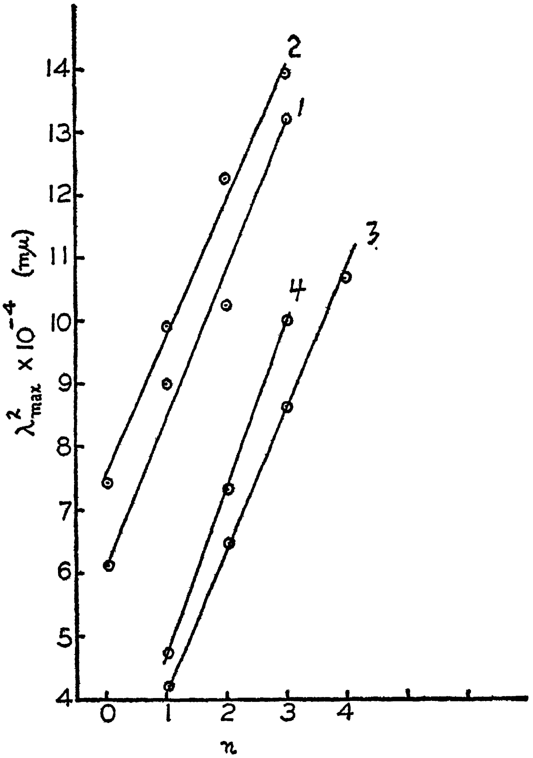
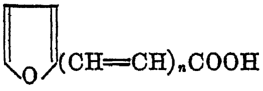
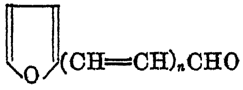


Fig. 4a. A plot of λ^2_{max} against the number of ethylenic bonds, n, in the linearly conjugated series:



Curve 1



Curve 2

$CH_3(CH{=}CH)_nCOOH$

Curve 3

$CH_3(CH{=}CH)_nCHO$

Curve 4

each alkyl and each RCHOH— substituent was set equal to an increase of 2 and 6 mμ, respectively. In this manner the values of λ_{max} for a number of such compounds were calculated; a comparison with the observed values is shown in table 6. Although there are a few deviations of 10–15 mμ, many calculated values agree very closely with the observed ones.

There are a few exceptions among dyes of Class I: for instance, the p-dimethylaminophenylpolyenals, $(CH_3)_2NC_6H_4(CH{=}CH)_nCHO$ (158), the *p*-phenylenediamine Schiff bases of phenylpolyenals,

$$C_6H_5(CH{=}CH)_nCH{=}NC_6H_4N{=}CH(CH{=}CH)_nC_6H_5$$

(85), and the *p*-polyphenyls (97). For these three series it is found that a plot of λ^2_{max} against the number of ethylenic groups in the chain, *n*, gives a curve that is convex upward (figure 5). This is understandable in the case of the poly-

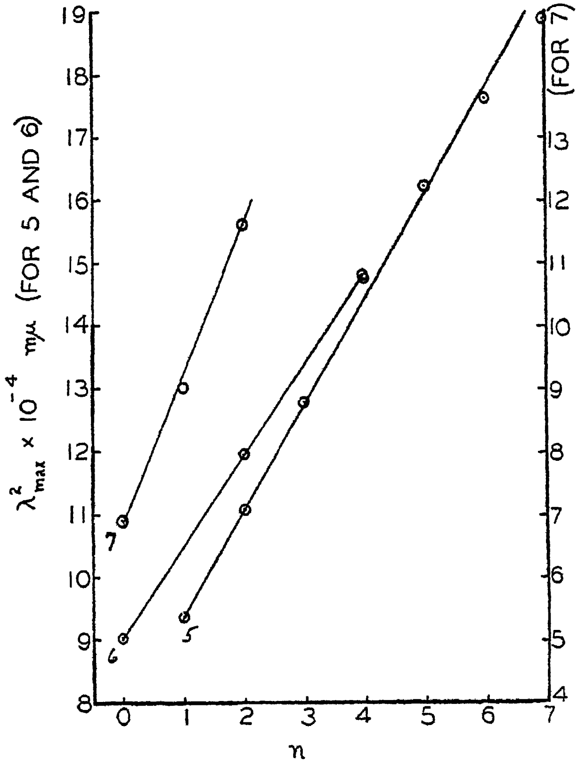
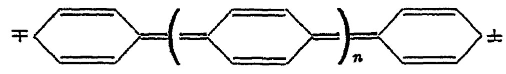


FIG. 4b. A plot of λ^2_{max} against the number of ethylenic bonds, *n*, in the linearly conjugated series: $C_6H_5(CH{=}CH)_nCHO$ (curve 5), $C_6H_5(CH{=}CH)_nCH{=}NN{=}CH(CH{=}CH)_nC_6H_5$ (curve 6), and $C_6H_5(CH{=}CH)_nCH{=}NC_6H_5$ (curve 7).

phenyls when one considers the resonance involved. The structures concerned in the absorption of light are of the type:



which contribute at the expense of the Kekulé resonance. When the number of phenyl groups is small, the percentage increase in length and contribution of these polar forms is sufficient to outweigh the additional energy required to overcome the Kekulé resonance, but as the number of phenyl groups increases, the percentage of contribution from polar forms (only two forms for each molecule while the number of Kekulé forms is 2^n) decreases. Hence, an increase in λ_{max} can be expected for each additional phenyl group, but the increase will diminish with increasing chain length. This amounts to an increase in the restoring force constant, k, with increasing n; this is contrary to the assumption that k is a constant.

TABLE 5

Observed and calculated values of λ_{max} for polyenes and polyenynes

n	λ_{max} (OBSERVED)	λ_{max} (CALCULATED)	COMPOUND	REFERENCE
	$m\mu$	$m\mu$		
1	190	155	$CH_2{=}CH_2$	(279)
2	217	(217)	$CH_2{=}CHCH{=}CH_2$	(278)
	219		$CH_2{=}CHCH{=}CH_2$	(172)
3	260	(265)	$CH_2{=}CHCH{=}CHCH{=}CH_2$	(161)
	257		$CH_2{=}CHCH{=}CHCH{=}CH_2$	(160)
	264		$CH_3CHOHCH{=}CHC{\equiv}CC(CH_3){\equiv}CHCH_3$	(110)
	253		$CH_2{=}C(CH_3)C{\equiv}CC(CH_3){=}CH_2$	(15)
4	302	305	$CH_2{=}CH(CH{=}CH)_2CH{=}CH_2$	(161)
	320		$CH_3(CH{=}CH)_4CH_3$	(20, 166)
	305		$CH_3CHOH(CH{=}CH)_3C{\equiv}CH$	(110)
	311		$CH_3(CH{=}CH)_4CH_2OH$	(110, 253)
5	341	341	$CH_3CHOH(CH{=}CH)_2C{\equiv}C(CH{=}CH)_2CHOHCH_3$	(110)
6	375	372	$CH_3(CH{=}CH)_6CH_3$	(166)
	386		$HOOCCH(CH_3)CH{=}CHCH{=}C(CH_3)(CH{=}CH)_2{-}C(CH_3){=}CHCH{=}CHCH(CH_3)COOH$	(110)
7	392	403	$[CH_3CHOH(CH{=}CH)_3C{\equiv}]_2$	(110)
8	431	431	$[CH_3OOCCH_2(CH{=}C(CH_3)CH{=}CH)_2]_2$	(110)
	420 (445)		Dihydro-β-carotene	(142)
9	466 (497)	457	β-Carotene	(80)
	502		*trans*-Bixindialdehyde	(165)
10	445 (475)	482	α-Carotene	(142)
	474 (507)		Violaxanthin	(143)
11	517	505	Lycopene	(80, 107, 165)
	495		γ-Carotene	(165)
	521		β-Carotene	(142)

Class II: Dyes to be included in this class are those for which there are two

TABLE 6*

Observed and calculated values of λ_{max} for compounds containing two or three conjugated $C{=}C$ *or* $C{\equiv}C$ *bonds*

λ_{max} (OBSERVED)	λ_{max} (CALCULATED)	COMPOUND
Two conjugated groups†		
$m\mu$	$m\mu$	
230	228	$CH_3(CH{=}CH)_2CHOHC{\equiv}CH$
229	228	$CH_3(CH{=}CH)_2CHOHC{\equiv}CCHOH(CH{=}CH)_2CH_3$
225	225	$CH_3CH{=}CHCHOHC{\equiv}CC(CH_3){=}CHCH_3$
224	223	$CH_3CH{=}CHCHOHC{\equiv}CCH{=}CH_2$
225	224	$CH_3CH{=}CHCHOHC{\equiv}CC(CH_3){=}CH_2$
223	223	$CH_3CHOHCH{=}CHC{\equiv}CH$
228	229	$CH_3(CH_2)_2CHOHC{\equiv}CCH{=}CHCHOHCH_3$
224	229	$C_6H_5CHOHC{\equiv}CCH{=}CHCHOHCH_3$
225	229	$CH_3OC_6H_4CHOHC{\equiv}CCH{=}CHCHOHCH_3$
229	229	$CH_3CH_2C(OH)(CH_3)C{\equiv}CCH{=}CHCHOHCH_3$
228	229	$CH_3CH{=}CHCHOHC{\equiv}CCH{=}CHCHOHCH_3$
228	225	$CH_3(CH_2)_3C{\equiv}CC(CH_3){=}CHCH_2OH$
228	225	$CH_3(CH_2)_3C{\equiv}CC(CH_3){=}CHCHOHCH_3$
228	225	$CH_3(CH_2)_3C{\equiv}CC(CH_3){=}CHC(OH)(CH_3)_2$
223	223	$(CH_3)_2C(OH)CH{=}CHC{\equiv}CH$
224	224	$CH_3CHOHC(CH_3){=}CHC{\equiv}CH$
220	220	$CH_3CH{=}C(CH_3)C{\equiv}CH$
227	227	$CH_3CH{=}CHCH{=}CHCH_3$
226	224	$CH_3(CH_2)_3C{\equiv}CCH{=}CHCHOHCH_3$
228	225	$CH_3(CH_2)_2CHOHC{\equiv}CC(CH_3){=}CHCH_3$
225	225	$CH_3CH{=}CHCHOHC{\equiv}CC(CH_3){=}CHCH_3$
223	223	$CH_3CHOHCH{=}CHC{\equiv}CH$
226	224	$CH_3CHOHCH{=}CHC{\equiv}C(CH_2)_3CH_3$
Three conjugated groups		
260	(265)	$CH_2{=}CHCH{=}CHCH{=}CH_2$
272	275	$CH_2{=}C(CH_3)CH{=}CHC(CH_3){=}CH_2$ (148)
276	275	$CH_3(CH{=}CH)_3CH_2OH$
278	275	$CH_3(CH{=}CH)_3CHOHC{\equiv}CH$
260	270	$CH_3CHOH(CH{=}CH)_2C{\equiv}CH$
264	263	$CH_3CHOHCH{=}CHC{\equiv}CC(CH_3){=}CHCH_3$
280	265	$CH_3CHOHCH{=}CHC{\equiv}CCH{=}CHCHOHCH_3$
281	276	$CH_3(CH{=}CH)_3CHOHC{\equiv}CCHOH(CH{=}CH)_3CH_3$
264	263	$CH_3CHOHCH{=}CHC{\equiv}CC(CH_3){=}CHCH_3$
259	259	$CH_3CHOHCH{=}CHC{\equiv}CCH{=}CH_2$
259	261	$CH_3CHOHCH{=}CHC{\equiv}CC(CH_3){=}CH_2$
279	265	$CH_3CHOHCH{=}CHC{\equiv}CCH{=}CHCHOHCH_3$
264	263	$CH_3CHOHCH{=}CHC{\equiv}CC(CH_3){=}CHCH_3$
255, 269	259	$CH_2{=}CHC{\equiv}CCH{=}CH_2$ (78)

* Values for compounds not listed in table 5 are from reference 110.

† Braude (34) reports three maxima for a conjugated diacetylenic compound, 2,7-dimethylocta-3,5-diyn-2,7-diol, at 229, 241, and 256 mμ.

or more nearly equivalent canonical structures, such as is found for those of types 4 and 5 above. The dye molecules will resonate chiefly among the two or more

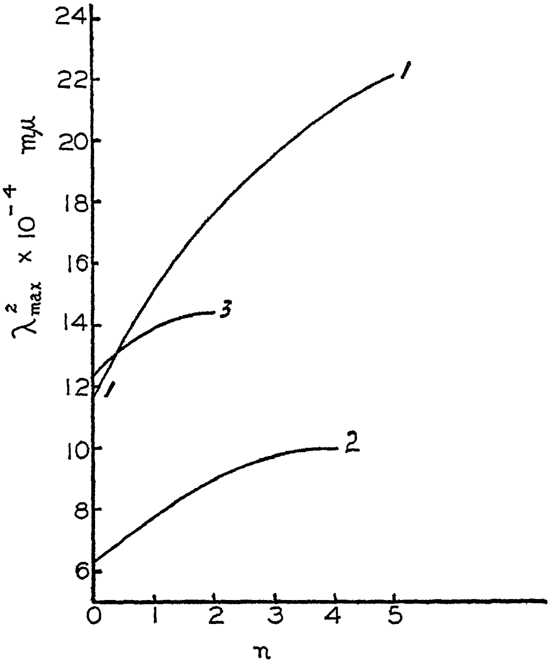
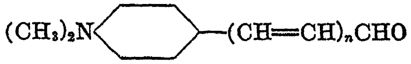
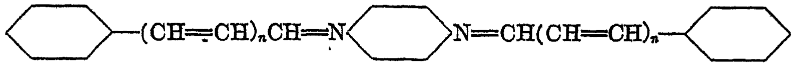


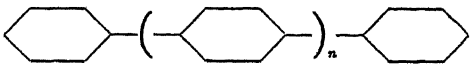
FIG. 5. A plot of λ^2_{max} against the number of ethylenic groups for the homologous series:



Curve 1



Curve 2



Curve 3

nearly equivalent structures but only by passing through many less stable structures (226), such as, for example, forms XV.

$$R_2N—CH{=}CH—CH{=}CH—CH{=}\overset{+}{N}R_2$$

XIV

$$\left\{\begin{array}{l} R_2N—CH{=}CH—CH{=}CH—\overset{+}{C}H—NR_2 \\ R_2N—CH{=}CH—\overset{+}{C}H—CH{=}CH—NR_2 \\ R_2N—\overset{+}{C}H—CH{=}CH—CH{=}CH—NR_2 \end{array}\right\}$$

XV

$$R_2\overset{+}{N}{=}CH—CH{=}CH—CH{=}CH—NR_2$$

XVI

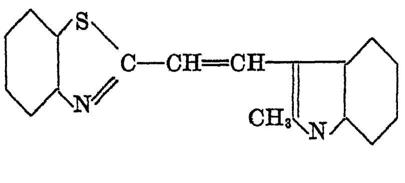
The transition of the molecule from one extreme structure—say, for example, XIV—to the other nearly equivalent structure, XVI, involves a great motion of electrons and this amounts to two facts: (*1*) that the molecule will be easily polarizable; (*2*) that the electronic oscillations will extend practically to the ends of the molecule. Lewis and Calvin (182), in their summary on the rules for absorption, point out that the determining factors of color are (*1*) the number of electrons involved (which is dependent upon the length of the conjugated system and the amount of effective charge transported) and (*2*) the electron mobility, i.e., the induced polarization (polarizability) rather than the permanent dipole moment.[15] Several authors have shown that there is no simple relationship between λ_{max} and the polarity of chromophores (116).

For dyes of Class II the color will deepen rapidly with increasing length of the molecule. When the molecule passes from one of the equivalent classical structures to the other, each carbon–carbon bond changes from a double to a single bond or from a single to a double bond, and since both structures are equally probable each carbon–carbon bond is identical. Therefore, the electronic oscillations throughout the molecule can be treated as a longitudinal wave along a string for which the frequency will be inversely proportional to the length. Lewis and Calvin (182) illustrated that this is so by obtaining a straight line when they plotted the number of double bonds in several cyanine dyes against λ_{max}, as measured by Brooker and coworkers (45) and Fisher and Hamer (19, 88; see also 157).

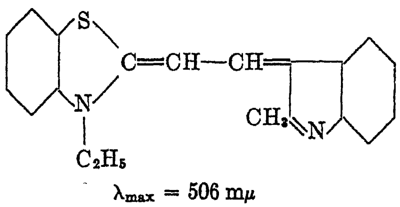
The difference, then, between dyes of Class I and dyes of Class II is the way λ_{max} varies with the length of the conjugated system. For Class I, the square of λ_{max} varies linearly with the length; for Class II, the first power of λ_{max} is a straight-line function of the length of the molecule.

---

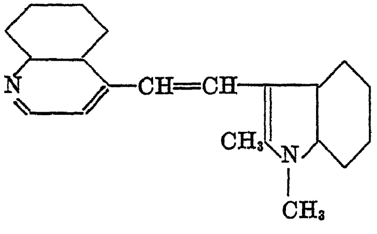
[15] Brooker and coworkers (48) have found for a pair of similar dyes that the more deeply colored have by far the larger dipole moment.



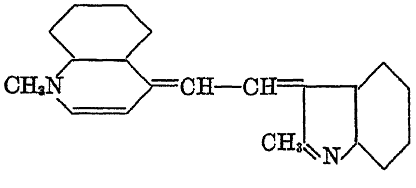
$\lambda_{max} = 392\ m\mu$
$\mu = 4.06 \times 10^{18}$



$\lambda_{max} = 506\ m\mu$
$\mu = 7.68 \times 10^{18}$

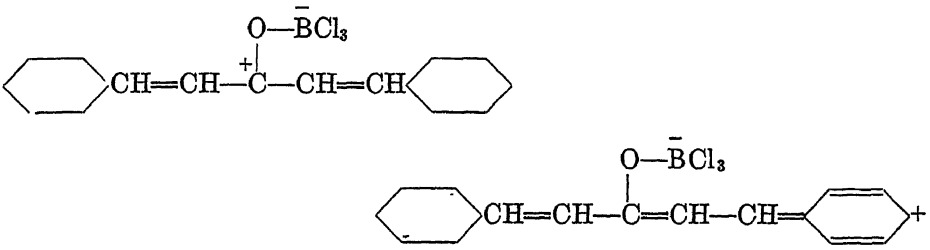


$\lambda_{max} = 394\ m\mu$
$\mu = 5.43 \times 10^{18}$

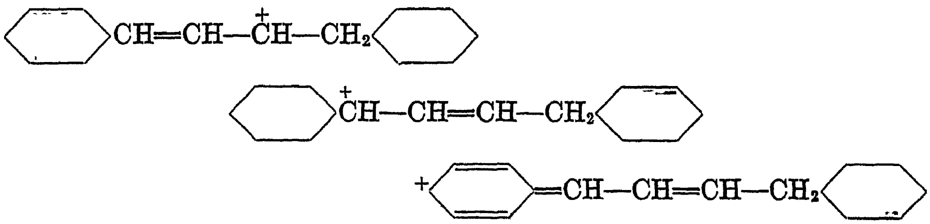


$\lambda_{max} = 616\ m\mu$
$\mu = 10.6 \times 10^{18}$

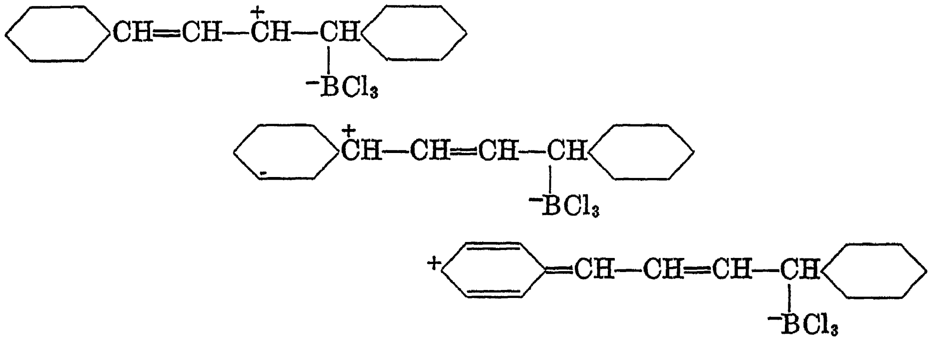
A dye of one class may change to become one of the other class. For instance, the polyenes (106, 166, 168, 188, 234), the polyenones (13, 233), and the carotenoids (80, 208) of Class I fall into Class II when placed in acid media such as $H^+_{\text{concd.}}$, stannic chloride, boron trichloride, etc. This is probably due to resonance among structures of near equivalence, such as, for a ketone



or for a polyene,



and



which cause the molecule to have a large polarizability. The anhydrobases of the benzothiazine dyes change from Class II to Class I upon removal of the alkyl halide. This change is quite prominent in figure 6.

Brooker (44) has spoken of dyes which are classified here in Class I as belonging to convergent series, since with increasing number of ethylenic groups the difference in λ_{max} between each successive member decreases, while dyes of Class II, he has said, form non-convergent series, for the difference in λ_{max} between successive members remains constant. This point is illustrated in figure 6.

The discussion so far of dyes of Class II has been limited to those dyes which have two classical structures of nearly equal potential energy. One may also

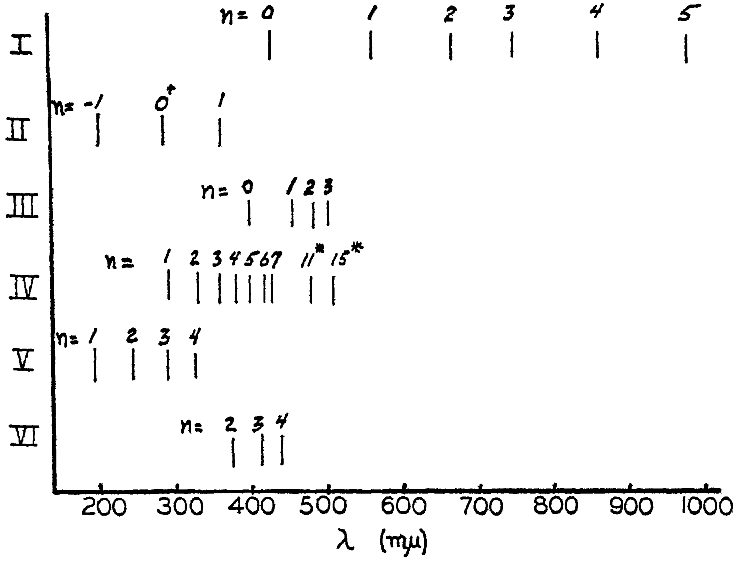
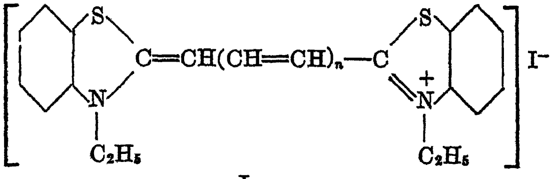


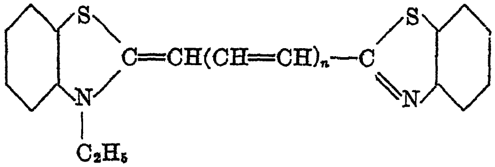
FIG. 6. Absorption maxima of homologues of dyes I (275) and II (272) in Class II and of dyes III (48), IV (107), V (107), and VI (144) in Class I.



I

$CHO(CH{=}CH)_nCH{=}CH{-}O^-$

II



III

$C_6H_5(CH{=}CH)_nC_6H_5$

IV

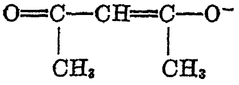
$CH_3(CH{=}CH)_nCOOH$

V

$C_6H_5(CH{=}CH)_nCOCO(CH{=}CH)_nC_6H_5$

VI

+, value for



$$O{=}\underset{CH_3}{C}{-}CH{=}\underset{CH_3}{C}{-}O^-$$

* Estimate by Henrici (115) for measurement by Kuhn (164).

consider examples where these two structures will not be equivalent. The λ_{max} of an unsymmetrical dye of type 4 above, $R''N(CH{=}CH)_nCH{=}\overset{+}{N}R'_2$, might be expected to be the arithmetic mean of the two related symmetrical dyes:

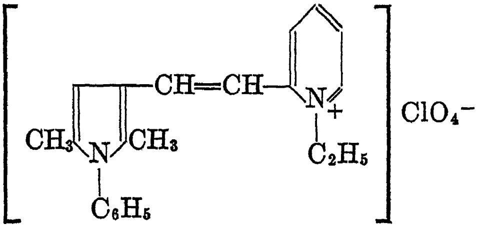
$$R''_2N(CH{=}CH)_nCH{=}\overset{+}{N}R''_2 \quad \text{and} \quad R'_2N(CH{=}CH)_nCH{=}\overset{+}{N}R'_2$$

Brooker (44) and coworkers, and also Fisher and Hamer (19), have found that this is not true in the case of a large number of cyanine dyes.

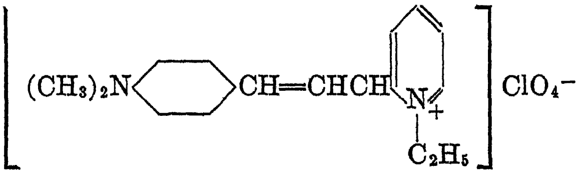
From one of the fundamental postulates of the resonance theory, that the more nearly equivalent are the resonant forms in potential energy the greater will be the resonance energy, one may state that the more equal in energy are the two end groups of the cyanine dyes when carrying the positive charge, the greater will be the resonance in the excited state and therefore the larger will be λ_{max}. Thus, if the two classical structures of the unsymmetrical dye

$$R_2''N(CH{=}CH)_nCH{=}\overset{+}{N}R_2' \quad \text{and} \quad R_2''\overset{+}{N}{=}CH(CH{=}CH)_nNR_2'$$

are not nearly equivalent, its λ_{max} will fall short of the arithmetic mean of the λ_{max} of the two related symmetrical dyes, and further, the greater the difference in stability of the two forms the greater will be this deviation[16] from the mean. In this connection Brooker *et al.* (45) have measured the spectra of a number of cyanines which are of two families: one, the pyrrole dyes, wherein various groups are paired with the *N*-phenyl-2,5-dimethylpyrrole group and the other, the styryl dyes, in which these same groups are paired with the *N*,*N*-dimethylaniline ring. Two examples are:



Pyrrole dye



Styryl dye

Upon arranging the dyes in each family in order of their increasing *deviation* the sequence of the second end groups in each family is practically the same. This is illustrated in figure 7.

Brooker has given some justification for the observed order by considering the relative stabilities of these groups according to resonance theories, which he calls the "additional double-bond stabilization" factor, and also by comparing the relative basic strengths of two or three of these groups as determined by other physical measurements. Also in this connection, Brooker and his collaborators

---

[16] Following Brooker's terminology reference has been made to this deviation of λ_{max} from the arithmetic mean of the λ_{max} of the two related symmetrical cyanines by simply calling it the *deviation*.

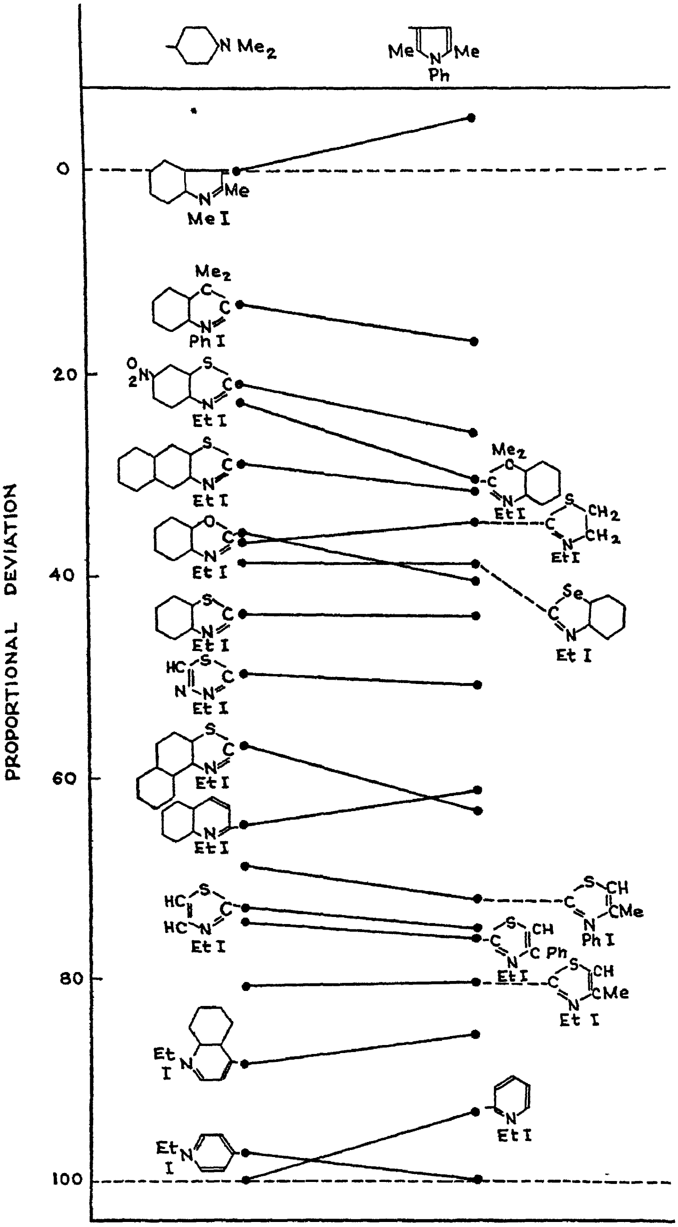
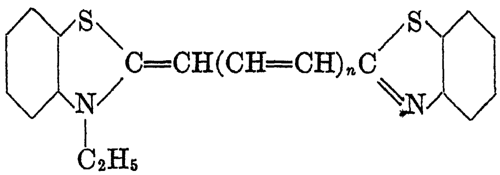
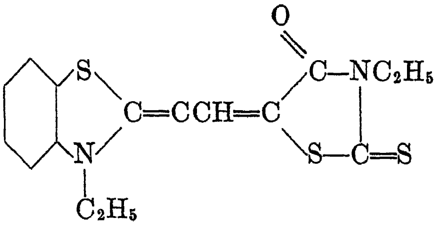


Fig. 7. Comparison of the *deviations* in two series of cyanine dyes. The relative *deviations* shown in the left-hand column are those of the styryl dyes; those on the right are of the pyrrole dyes. Reprinted from reference 44 through the courtesy of Interscience Publishers, Inc., and Dr. L. G. S. Brooker.

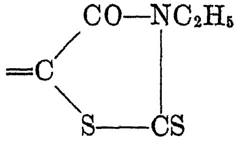
studied the spectra of two families of dyes which belong in Class I. These were the anhydronium bases, such as, for example:



and the merocyanines, as, for instance:



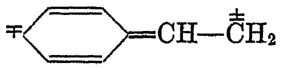
Both homologous series were found to be convergent, i.e., $\lambda_{\max}$ varies linearly with n, but only the merocyanines were studied to ascertain the *deviations*. The relative order of nine different groups paired with the



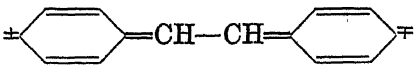
group agrees with that of the pyrrole and styryl dyes, with two exceptions.

VIII. STERIC HINDRANCE AND COLOR

The effects of steric hindrance upon the color of a substance are largely due to its interference with the resonance of the compound, either when the molecule is in its ground state or when it is in one of its excited states. Because of steric hindrance, the resonance may be limited to certain portions of the molecule and thereby affect its potential energy, and of course, its $\lambda_{\max}$. For instance, consider the spectra of some substituted ethylenes, measured and discussed by Jones (135; see also 6). The $\lambda_{\max}$ for styrene, $C_6H_5CH{=}CH_2$ (240 mμ[17]) (87), is attributed to the resonance among such forms as



where one phenyl ring and the two ethylene carbon atoms are in the same plane (257). The resonance of *trans*-stilbene among such forms as



---

[17] Although this $\lambda_{\max}$ is smaller than that of benzene its intensity ($\log \epsilon \cong 4.0$) is large, while $\lambda_{\max}$ for benzene is of low intensity and, according to quantum mechanics, corresponds to a transition of low probability (220, 227, 281).

accounts for a larger λ_{max} (295 mμ) and requires that two phenyl rings and the ethylene carbon atoms be coplanar. On the other hand, since in *cis*-stilbene only one phenyl ring and the ethylene carbon atoms can be coplanar simultaneously, it would be expected to have a spectrum similar to styrene, or at least, λ_{max} would be smaller than that of the *trans* isomer; the latter expectation is found to be true. Also, α,β-dimethyl-*trans*-stilbene (6, 189) has a spectrum like that of styrene; this indicates that only one phenyl ring is coplanar with the ethylene carbon atoms. The same considerations apply to unsymmetrical diphenylethylene, and it is seen in figure 8 that interference between the ortho hydrogen atoms will force one phenyl ring to be rotated out of the plane of the paper. It should, and does, have a spectrum similar to that of styrene. Nevertheless, tri- and tetra-phenylethylenes may actually have two phenyl rings coplanar with the ethylene carbon atoms if one, or two, phenyl rings are simply rotated something less than 90° out of the plane (see figure 9). Hence, the two compounds would be expected to have, and do have, spectra similar to that of *trans*-stilbene. Jones (135) has divided these compounds into three groups: compounds which have spectra similar to that of styrene, compounds which have spectra similar to that of *trans*-stilbene, and compounds which have spectra intermediate between these two extremes.

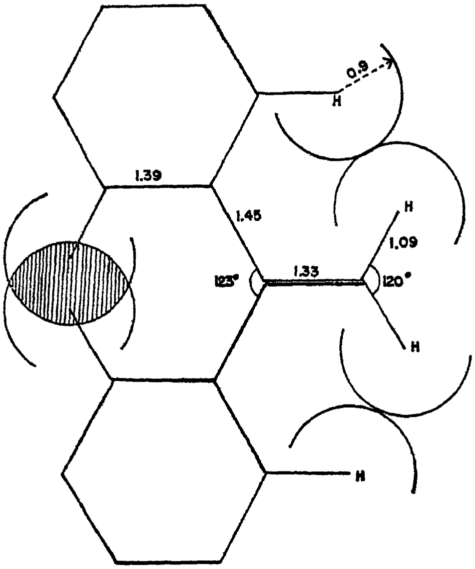


FIG. 8

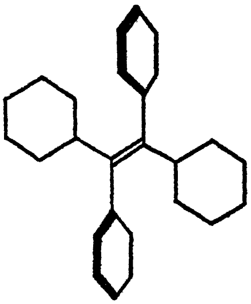


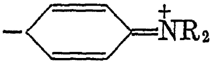
FIG. 9

FIG. 8. *as*-Diphenylethylene. Diagram illustrating interference between ortho hydrogen atoms. Reprinted from reference 135 through the courtesy of the Editor, Professor Arthur B. Lamb, and the Mack Printing Company.

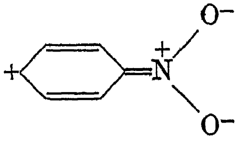
FIG. 9. Tetraphenylethylene

"STYRENE" TYPE OF SPECTRA	INTERMEDIATE SPECTRA	"*trans*-STILBENE" TYPE OF SPECTRA
Styrene	*cis*-Stilbene	*trans*-Stilbene
α,α-Diphenylethylene	α-Methylstilbene	Triphenylethylene
α,β-Dimethyl-*trans*-stilbene		Tetraphenylethylene

Steric strain, arising in the molecule when it is excited to the electronically excited states, would increase the potential energy of these higher states and therefore, according to equation 1, would increase the frequency of the absorbed light (225, 275). This has been illustrated by Remington (255) in the case of substituted *N*,*N*-dimethylanilines. Their ionic resonant forms are of the type

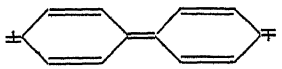


in which the ring, the nitrogen atom, and the methyl carbon atoms must be coplanar. When groups are situated in the ortho positions of the ring there is a spatial interference to such coplanarity and, as expected, there results a hypsochromic shift in λ_{max} (29, 136). Thus, 2-methyl- and 2,6-dimethyl-*N*,*N*-dimethylanilines have successively smaller λ_{max}, a fact which is illustrated in figure 10. Further, upon increasing the size of the ortho group these effects should become more pronounced. This is found true for *o*-*tert*-butyl-*N*,*N*-dimethylaniline, whose λ_{max} is close to that of the *o*,*o*-dimethyl-substituted derivative, and also for the *o*-halogenated *N*,*N*-dimethylanilines, whose values for λ_{max} decrease in the order of increasing size of the halogen atoms. Similar steric effects result when groups are ortho to the nitro group (40a, 209), causing a hindrance to the coplanarity of the oxygen atoms in such resonating structures as

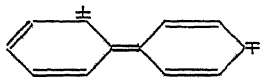


Remington found λ_{max} for *p*-nitro-*N*,*N*-dimethylaniline to diminish rapidly as one, and then two, methyl groups are placed ortho to the nitro group (see figure 10).

Several investigators (58, 113, 232, 235, 257, 276, 286, 301) have offered additional examples of steric hindrance occurring in the excited state of organic molecules, particularly the substituted biphenyls. It is found that 3,3′- or 4,4′-disubstituted biphenyls have spectra similar to that of biphenyl with, perhaps, anticipated substitutive effects. These spectra are thought to correspond to resonance among such forms as



and



where there occurs a double bond between the two rings. For 2,2′-disubstituted, and especially 2,6,2′,6′-tetrasubstituted biphenyls, the spectra are found to be similar to those of the correspondingly substituted benzenes. This is because the steric inhibition between the ortho groups prevents the coplanarity of the two phenyl rings, as would be required for the biphenyl-type resonance. As is to be expected, 9,10-dihydrophenanthrene (XIV) and 4,5-methylene-9,10-dihydrophenanthrene (XV), where the methylene bridges hold the two phenyl rings in a plane, have spectra similar to that of biphenyl (137).

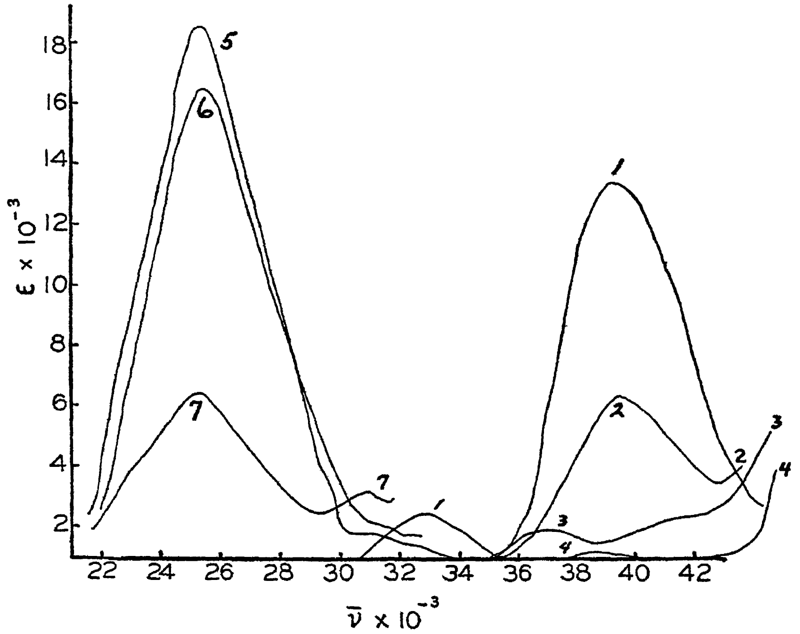
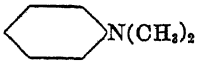
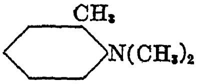


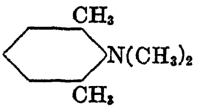
Fig. 10. Absorption spectra of dimethylanilines



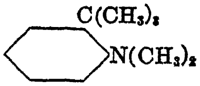
Curve 1



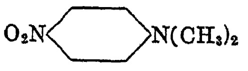
Curve 2



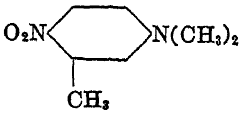
Curve 3



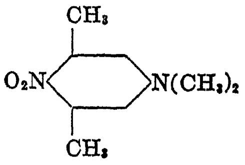
Curve 4



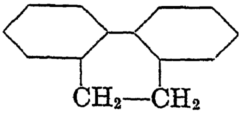
Curve 5



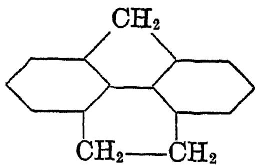
Curve 6



Curve 7

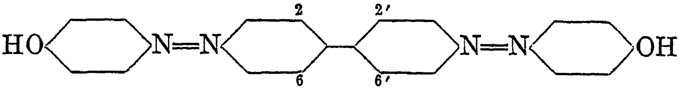


XIV



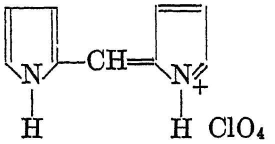
XV

Brode and Morris (42) have reported additional examples of this pinching off of the biphenyl conjugation in some bisazo benzidine dyes.

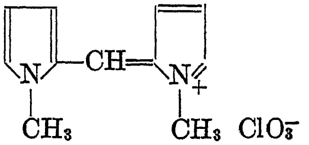


By introducing methyl groups into 2,2′-positions partial insulation of the two azo chromophoric systems was accomplished, and by tetrasubstitution into the 2,2′,6,6′-positions, complete insulation was effected, as evident from their absorption spectra.

Steric hindrance occurring in the ground state of the molecule will in general cause the molecule to absorb at longer wave lengths than a similar compound in which the steric strain does not exist. This is due to an increase in the potential energy of the ground state, bringing about a smaller difference in the energies of the ground and first excited states to allow a smaller excitation energy. An example of this was reported by Brunings and Corwin (50) and a number of additional examples were reported by Brooker *et al.* (47). For instance, Brunings and Corwin found that di-NH-dipyrrylmethene perchlorate (XVI) in chloroform has a λ_{max} at 470 mμ, while di-*N*-methyldipyrrylmethene perchlorate (XVII) in the same solvent has a λ_{max} at 510 mμ.



XVI



XVII

In dye XVI the two pyrrole rings could be coplanar only if there is a slight bending of the N—H bonds. When the hydrogen atoms are replaced by methyl groups, the methyl groups will overlap too much to allow the two pyrrole rings to lie in the same plane. This departure from planarity decreases the resonance in the ground state, bringing about a smaller difference in energies of the ground and first excited states and consequent absorption at longer wave lengths. Brooker and coworkers investigated this bathochromic effect due to crowding in several higher vinylogs of these two dyes and also with other symmetrical and unsymmetrical cyanine dyes. Just as it is found that the rate of racemization or the existence of optical isomers of ortho-substituted biphenyls does not depend solely upon the size of the ortho groups, so did Brooker and collaborators find that there is no simple relationship between the area of overlap in the projections of these cyanine dyes and the shift of λ_{max} to longer wave lengths.

IX. CHEMICAL CONSTITUTION AND THE SHAPE OF SPECTRA

The discussion, up to this point, has been confined to generalizations describing the position of absorption bands in the spectral range 200–800 mμ. Other points of concern about these spectra might be the number of bands appearing and the width, height, and shape of each band. It is worth while to review the correlations between chemical constitution and the shape and existence of several absorption bands for organic molecules.

A. Fine structure

It has been observed by a number of authors (204) that with a decrease in temperature the fine structure of absorption bands increases. This is illustrated in figures 11 and 12. This is in part due to a diminishing random distribution of the molecules in the various vibrational and rotational states by grouping in certain lower and lower vibrational states as the temperature falls. However, this is not the only factor, because in many instances a large decrease in temperature alters very little the fine structure, or broadness, of a band.[18]

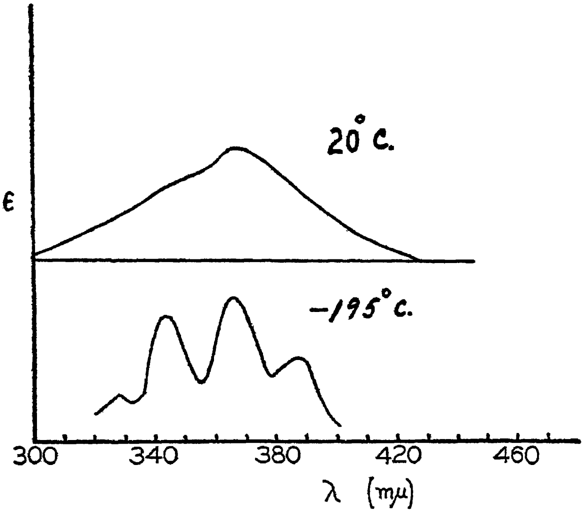


FIG. 11. Absorption spectrum of dodecapentaenic acid in ether–alcohol mixture at 20°C. and −196°C., measured by Hauser, Kuhn, and Seitz (107, page 403).

Suppose that immediately after the absorption of light the initial excited state passes into another excited state, or the electronic vibrational energy of the excited molecules is transformed into low-energy atomic vibrational, or rotational, energy; the probability of the latter process would be determined by the Franck–Condon principle. If this transformation takes place in 10^{-13} to 10^{-14} sec.,[19] then, according to Heisenberg's principle, there will be an uncertainty in the observed frequency of absorbed light by several hundred wave numbers; hence, a diffuse band will be observed. In order for a group to pick up this energy it must, first of all, be attached to the chain of atoms whose electrons are participating in the electronic oscillations. Lewis and Calvin (182) have called this the "loose-bolt" effect, whereby mechanical energy is dissipated through a loosely held, vibrating body. The readiness with which groups will absorb the electronic vibrational energy will be greater the larger their mass and the weaker their restraining forces.[20] Thus, for example, the fine structure of the benzene spectrum gradually disappears in passing over the spectra for fluorobenzene to iodobenzene, pictured in figure 13. Also, it may be noticed that the spectra of phenyl-substituted ethylenes (135) have broad absorption bands without the fine structure characteristic of the ethylene spectrum. On the other hand, compounds containing methylene bridges, such as are found in fluorene, fluorenone, anthrone, and hydrindene, which hold the molecule rigid, show increased fine structure over similar compounds that do not have the bridges (136, 138, 252). Similarly, condensed-ring structures are too rigid to allow low-energy group vibrations and the spectra of such compounds exhibit much fine structure, while

---

[18] Compare the explanations given by Rădulescu and collaborators (246, 247).

[19] This value has been chosen because when one divides the resonance energy of a conjugated diene by Planck's constant, *h*, one obtains this number having the dimensions of time and, which one may consider, gives the order of magnitude of the time required to establish in the excited molecule the conditions of the resonance state (182).

The "natural width" of the band may also be due to a large number of low-frequency vibrational states in the upper electronic level so as to appear almost as a continuum of energy, or to perturbations upon the absorbing molecules from electric and magnetic fields of solvent molecules so as to greatly increase the number of neighboring excited states (32).

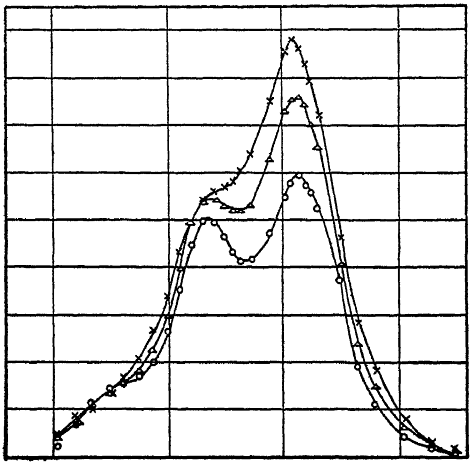
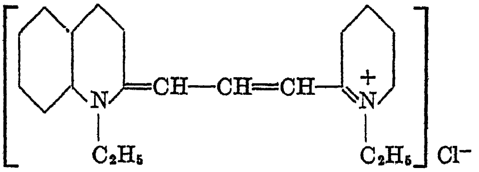


FIG. 12. Absorption spectrum of



at 298° K. (×), at 202°K. (△), and at 108°K. (○). Reprinted from an article by S. E. Sheppard and H. R. Brigham (J. Am. Chem. Soc. **66**, 381 (1944)) through the courtesy of the Editor, Professor Arthur B. Lamb.

---

[20] Lewis and Calvin point out that the ability of substances to quench fluoresence closely parallels the absence of fine structure from their spectra.

the substituted derivatives may have spectra which resemble that of the parent hydrocarbon but with a slight broadening of the peaks (136).

It is interesting to consider the spectra of acetone, biacetyl, and triketopentane, measured and discussed by Calvin and Wood (59), among which only the spectrum of biacetyl shows fine structure (figure 14). First of all, the resonance of biacetyl which accounts for the bathochromic shift of its λ_{max} over the λ_{max} of acetone is due to the structures

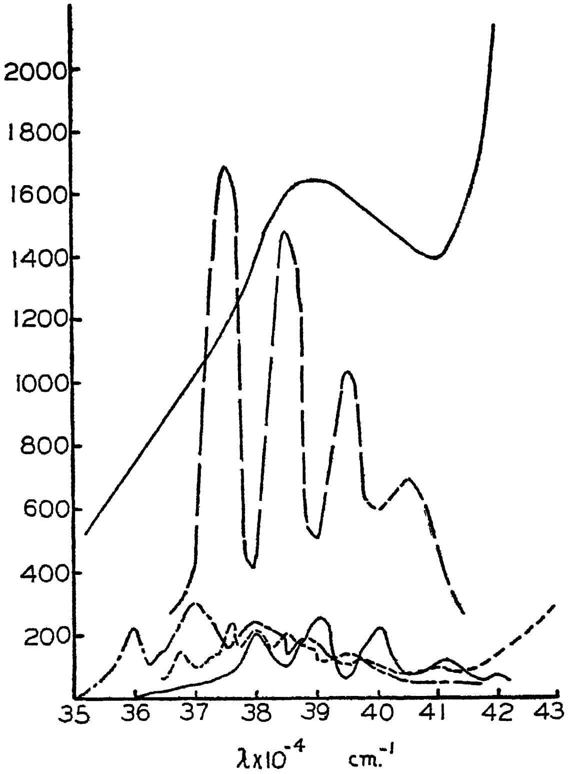
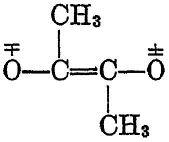


FIG. 13. Absorption spectra of benzene and halobenzenes

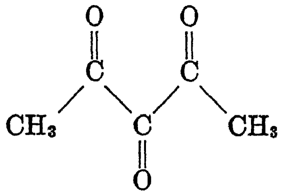


$$\overset{\mp}{O}-\underset{}{\overset{CH_3}{\overset{|}{C}}}=\underset{\underset{CH_3}{|}}{C}-\overset{\pm}{O}$$

(supported by the fact that the distance between carbonyl carbon atoms is only 1.47 Å.). The acetone band does not exhibit fine structure because fo the "loose-bolt" effect of the methyl groups, whereby the electronic vibrational energy is transformed into low-energy rotational energy.[21] However, the excitational energy for biacetyl is presumably too low to cause group vibrations or rotations and the spectrum shows fine structure. On passing to triketopentane, Calvin and Wood have explained that its most stable coplanar configuration is

---

[21] The energy barrier to "free rotation" of the methyl groups of acetone has been estimated to be only about 1 kg.-cal. (268).



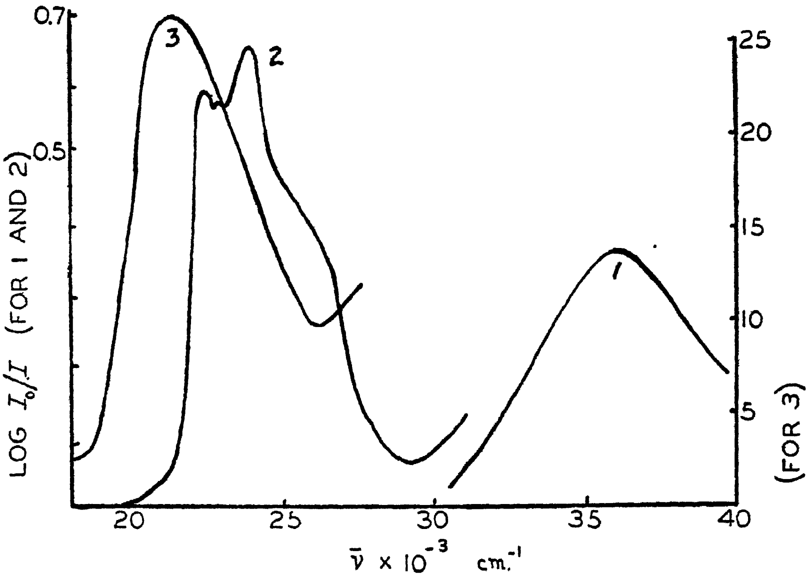
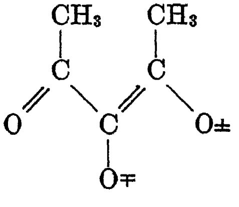
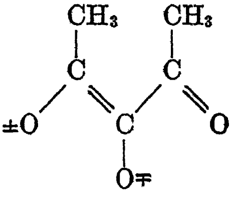

0.7
0.5
LOG I_0/I (FOR 1 AND 2)
25
20
15
10
5
(FOR 3)
3
2
1
20
25
30
35
40
$\bar{\nu} \times 10^{-3}$ cm.$^{-1}$

FIG. 14. Absorption spectra of acetone in hexane at room temperature (curve 1), biacetyl in hexane at room temperature (curve 2), and triketopentane in isoöctane at −50°C. (curve 3). Redrawn from reference 59 through the courtesy of the Editor, Professor Arthur B. Lamb.

Owing to the coulombic repulsion between the neighboring oxygen atoms there will be a tendency for one acetyl group to rotate out of the plane of the paper, resulting in a low energy for rotation. With a larger mass than just that of the methyl group, the acetyl group readily dissipates the electronic vibrational energy through group rotational energy and destroys any fine structure. Since the planar configuration necessary to permit the linear oscillation





is impossible, the electronic oscillation extends through only two carbonyl groups and gives a λ_{max} close to that of biacetyl.

The absorption spectra of all unsaturated hydrocarbons contain a group of narrow intense bands in the Schumann region which has been interpreted as the first member of a Rydberg series (64, 65, 241). In addition, these hydrocarbons have a long-wave-length absorption band. For a few hydrocarbons these bands show vibrational structure very similar to that in the Schumann region, and Miss E. P. Carr has found it possible to select comparable points for determination of the energy difference between the two electronic levels. These *Rydberg transition* bands differ from the usual molecular electronic transition bands and may be distinguished by the fact that the former are not appreciably displaced by conjugation of double bonds (64).

On the basis of her interpretation of these long-wave-length bands of the hydrocarbons as due to a Rydberg transition, Miss Carr was able to calculate resonance energies directly from spectra (62). The values for benzene and the cyclohexadienes are in satisfactory agreement with those calculated from thermal data, but there is a wide difference between the thermal and spectral values for cyclopentadiene.

B. Partials

Insulated resonating systems or insulated chromophores will have disjoined electronic oscillations, giving rise to excited states of different energies and, hence, separate absorption bands. Such bands from localized oscillations have been called *partials* (27, 182, 214, 215). This is somewhat related to the section above wherein the insulation of chromophores was discussed. In this respect, it has been observed that molecules of the type $A(CR_2)_nB$, in which A and B are insulated from one another, have spectra approximately the same as solutions of equimolar mixtures of ACR_2H and BCR_2H (39, 95, 139).

A noteworthy example of *partials* is found in the case of the carotenoids studied by Zechmeister and his coworkers (308–312). They found that when an all-*trans* carotenoid is isomerized into a mixture of *cis–trans* isomers, three spectroscopic changes occur: (*a*) the maximum in the visible shifts toward shorter wave lengths, (*b*) a new band appears in the ultraviolet region, referred to as a *cis* peak, and (*c*) the fine structure is diminished. If the double bond about which two portions of the molecule are *cis* acts as an insulating group, such that the electronic oscillations on each side are partially isolated from one another, then these *cis* peaks may be interpreted as *partials*. For short molecules the *cis* peak will be displaced not far from the band for the *trans* isomer but for long molecules it may. Thus, Sandoval and Zechmeister (259) found that the conversion of *trans*-diphenylbutadiene into the *cis* isomer is accompanied by the gradual disappearance of a band at 328 mμ, with the simultaneous appearance of a new one at 313 mμ. On the other hand, the *cis* peak for the long carotenoids appears at shorter wave lengths than the *trans* maximum by 100–150 mμ. Zechmeister, and his collaborators, have also reported that a stereoisomer showing a very high *cis* peak must possess a *cis* double bond near the center of the conjugated system and that as a rough approximation the intensity of the *cis* peak can be taken proportional to the square of the distance between the center of the chromophore and the midpoint of the straight line between its two ends (309). In addition, they find that each *trans* → *cis* rotation causes a decrease in the wave length of the fundamental band (311) by 5 mμ and that the difference in the λ_{max} for a stereoisomer and that of the all-*trans* form will give a rough indication of the number of *cis* double bonds (310).

A *cis* double bond is not a complete insulator but merely inhibits the electronic oscillation throughout the length of the conjugated system and sets up a shorter vibrating system which stops at the *cis* double bond. This means that the potential energy of the excited state, corresponding to the resonance of the completely conjugated system, is greater; hence there is a hypsochromic shift in the position of the fundamental band, but also there are created new, higher excited states corresponding to the "isolated" oscillating systems which give rise to new bands (*partials*) at shorter wave lengths.

The nitro group occasionally exhibits a *partial* band which may overlap with the main absorption band of the molecule. Several authors have noted this (169).

Often bands have a shoulder which Lewis and coworkers (187) attribute to (*1*) partial resolution of fine structure, (*2*) neighboring *partial* electronic levels, or (*3*) two isomers in rapid equilibrium. They point out that the shoulder on the long-wave band for methylene blue is due to the second, while that of crystal violet is due to the third.

C. y-Bands

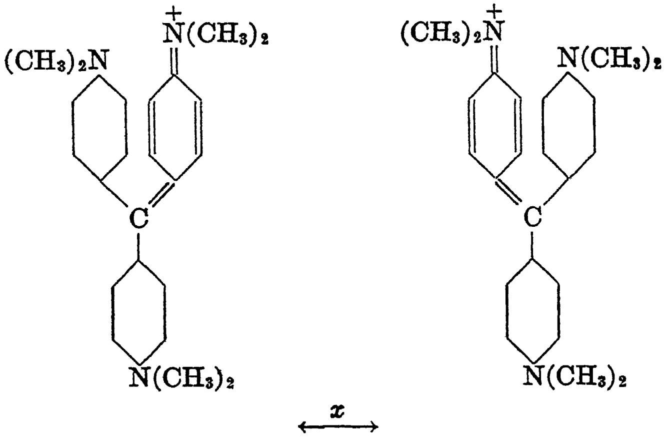
If a molecule has a conjugated system extending in more than one dimension there may be two, or even three, optical axes. When such a molecule absorbs light there will be electronic oscillations along these optical axes giving rise to excited states of different potential energies and, hence, absorption bands of different frequencies. Lewis and Calvin[22] have associated the band of lowest frequency with the direction of longest extension in the molecule and called it the x-band. The band corresponding to the axis at right angles to this major axis has been called the y-band. Usually the x-axis for a molecule can be predetermined from its structural formula and frequently there will be just one axis, as is true for the linearly conjugated molecules. For dyes of the triphenylmethane and methylene blue type this may be a little less obvious.

The existence of x- and y-bands may be surmised when one considers the spectra of dyes related to malachite green (182).[23] The x- and y-bands for crystal violet should merge into one, since the two axes are identical.

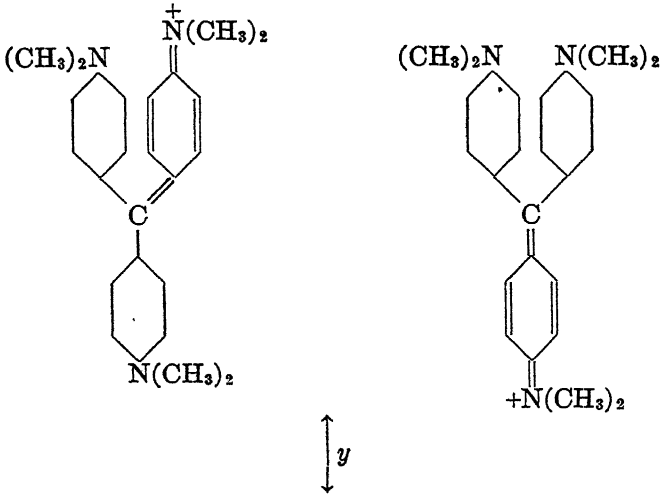
---

[22] See also the fine discussion of x-, y-, and x'-bands by Branch, Colbert, and coworkers (33, 145, 287, 288).

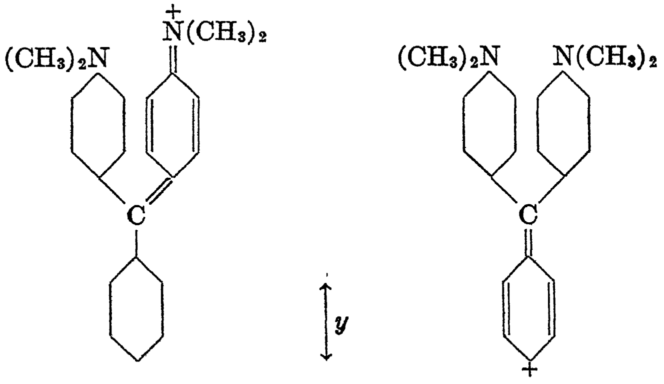
[23] From quantum-mechanical considerations Forster (92) has concluded that malachite green should have two bands to the one of crystal violet. Note also the discussion of Henrici (115) concerning optical axes normal to one another.



and



On the other hand, malachite green should have an x-band of about the same wave length as crystal violet but a y-band of smaller wave length, owing to the fact that the resonance in the y-direction involves a carbonium carbon atom which is of lower stability than an ammonium nitrogen atom.



Now if an auxochrome which readily accepts a positive charge (NR_2 or OCH_3) is placed on the lower phenyl group, this should not affect appreciably the position of the *x*-band but increase the wave length of the *y*-band; conversely, an auxochrome which prefers a negative charge (NO_2) should lower the wave length of the *y*-band to a lower value than is found for malachite green. Finally, the loss of the *y*-axis, by the removal of the lower phenyl group, as is the case for Michler's hydrol,

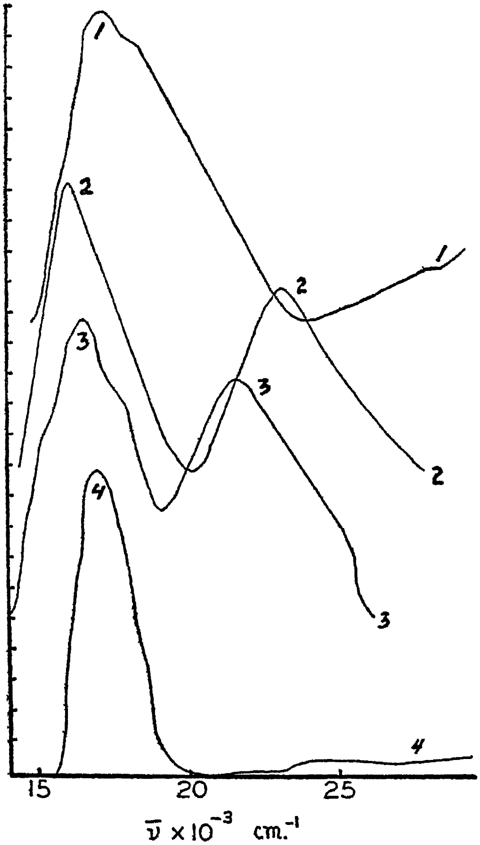
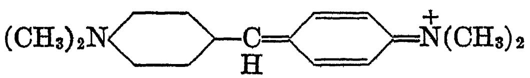


FIG. 15. Absorption spectra of crystal violet (curve 1), malachite green (curve 2), *p*-methoxymalachite green (curve 3), and the ion of Michler's hydrol (curve 4). 1, 2, and 3 in ethanol; 4 in glacial acetic acid; all at room temperature (179).

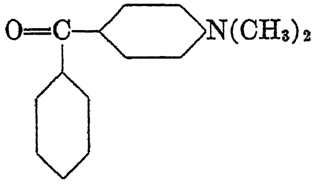


should result in the absence altogether of the *y*-band. These predictions are found to be correct and are illustrated in the spectra pictured in figure 15.

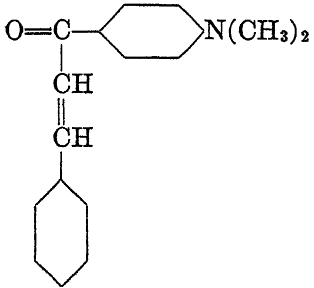
The strongest evidence for the existence of *x*- and *y*-bands is supplied through the use of polarized light. Lewis and Bigeleisen (179, 181) produced oriented dye molecules in a rigid solvent and found the absorption of light to be a maximum when light of the same wave length as that of the *x*-band of malachite green was polarized parallel to the x-direction and a minimum when polarized at right angles to this. The opposite was found true for light of the same wave length as the y-band. That is, when its plane of polarization was parallel to the x-axis, the intensity of absorption was a minimum and a maximum when the light was polarized parallel to the y-direction.

Lewis and Bigeleisen (179) were also able to show by a different method that these second absorption bands for malachite green and fluorescein were y-bands. Weigert (297) had earlier found that when one irradiates a fluorescent substance in a rigid medium with polarized light it reëmits light polarized in the same direction. Wawilow (296) later discovered that if one uses polarized light in the near ultraviolet (of higher energy) there results the same fluorescent bands but the fluorescent light is polarized normal to the exciting light. Lewis and Calvin interpreted this to be due to an excitation by light of sufficient energy to carry the molecule to a higher excited state where the electronic oscillations will be in the y-direction. Before the molecule has time to reëmit its ordinary fluorescence it suffers partial quenching to drop to the first excited state. As a result of this process the y oscillations will change to x oscillations and the molecule will now reëmit light polarized in a different sense to that of the exciting light. Lewis and Bigeleisen (179) found that the maximum of this negative polarization nearly coincides with the maximum absorption in y-bands.

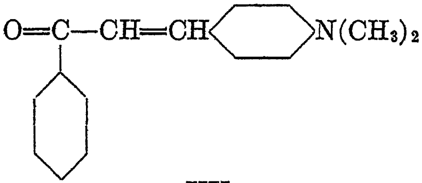
The direct demonstration of such oriented excitation offers considerable experimental difficulty, and more often the indirect approach is made as described above in the case of the crystal violet dyes. For example, Katzenellenbogen and Branch (146) studied the spectra of p-dimethylaminobenzophenone (XVIII) and two of its vinylogs, chalcones XIX and XX.



XVIII



XIX

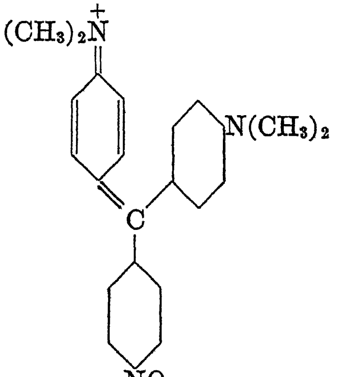


XX

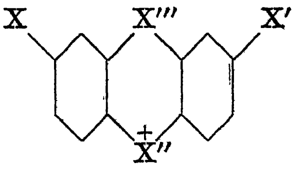
Katzenellenbogen and Branch point out that the direction parallel to the line joining the oxygen and nitrogen atoms in XVIII and XIX should be the axis of maximum polarizability in these molecules (x-band) and that one can say as a first approximation that in XX the ethylenic bond chiefly increases the polarizability along the x-axis, while in XIX it chiefly increases the polarizability along the y-axis. Hence, λ_x (λ_{max}) of XX should be greater than λ_x of XIX, and λ_y (λ'_{max}) of XIX should be greater than λ_y of XX. After studying the spectra of compounds XVIII, XIX, and XX, these authors observed that the interpolation of an ethylenic bond has the expected effect. They found λ_{max} for XX and XIX to be 419 and 387 mμ, respectively, and λ'_{max} to be 264 and 303 mμ, respectively. This same relationship between the wave lengths of the first and second absorption bands is found true also for several of the chalcones studied by Alexa (3).

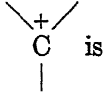
Another investigator to use this indirect method is R. N. Jones, who studied the spectra of derivatives of the polynuclear aromatic hydrocarbons (134, 136). Because of the closely packed structure of these molecules they do not exhibit such clearly defined x-bands and y-bands as do molecules such as triphenylmethyl ions and carotenoid dyes, in which the conjugated systems are along easily separated axes. Nevertheless, Jones finds in the spectra of these polynuclear compounds definite shifts in certain maxima so that one can correlate particular bands with electron excitations in a given direction.

Lewis (176) observed that the x-band of malachite green, λ_{max} = 621 mμ, increases for p-nitromalachite green



probably because the acidic nitro group reduces the amount of positive charge in the lower phenyl group, that is, increases the amount of positive charge oscillating horizontally in the two amino-substituted rings. On the other hand, a group like the NR_2 or OCH_3 group, attached to the lower phenyl ring, decreases the amount of positive charge oscillating horizontally by "side tracking" a portion of the positive charge into a vertical direction, and therefore λ_{max} will decrease. The order of this decrease is CH_3, OCH_3, NR_2. Meanwhile the y-band increases in wave length, until in crystal violet the x- and y-bands coincide. Lewis extended such considerations to other types of dyes the structures of which could be represented by the general structural formula,



and he set up a rule concerning the position of the x-band: namely, "since these molecules have approximately the same dimensions, the λ_{max} will be larger the greater is the amount of positive charge occurring on the auxochromes X and X'." Thus, with X and X' as OH, OR, O, NH_2, or NR_2, it is found that λ_{max} increases in the order given. If X''' is O, S, or NR, one observes a decrease in λ_{max} due to the acquisition of the positive charge part of the time by the oxygen, sulfur, or nitrogen atoms and consequent lowering of the positive charge on the auxochromes, X and X'. The replacement of CR by N at X'' is accompanied by a bathochromic shift, since  $\overset{+}{\mathrm{C}}$ is more stable than $\overset{+}{—\mathrm{N}—}$, and upon adding a proton to the nitrogen a still larger bathochromic shift occurs, for practically all of the positive charge remains on the X and X' groups.

Lewis studied such dyes as the six following types: triphenylmethane (X''' absent, X'' = CR), diphenylmethane (X''' absent, X'' = CH), xanthene (X''' = O, X'' = CR), acridine (X''' = NR, X'' = CR), oxazine (X''' = O, X'' = N), thiazine (X''' = S, X'' = N), and azine dyes (X''' = NR, X'' = N). Choosing malachite green for the reference molecule and following the observed empirical rule that "any change in X and X', or X'', or X''' produces the same changes in λ_{max} regardless of the character of the rest of the molecule," Lewis determined empirical constants for the shift in λ_{max} when making the above indicated substitutions for X, X', X'', and X'''. Upon comparing the λ_{max} calculated from these constants with the observed values for seventy dyes, excluding the acridine dyes,[24] the average deviation is 5 mμ.

D. *z-Bands*

In certain cases there will be found molecules with an appreciable polarizability in three directions whose spectra, according to the discussion in the above section, should have at least three maxima. Scheibe (261), and also Jelley (132), has studied the spectrum of pseudoisocyanine, and the x-, y-, and z-bands have been assigned as shown in figure 16. The band at 530 mμ is the x-band corresponding to the major axis in the plane of the molecule, the band at 490 mμ is the y-band corresponding to the minor axis in the plane of the molecule and perpendicular to the major axis, while the band at 573 mμ is the z-band arising through a polarization along the length of the *threads* of molecules. This z-band does not appear in dilute solutions of pseudoisocyanine. These *threads* are due to a face-to-face polymerization occurring in concentrated aqueous solution, wherein there probably exists an intramolecular electronic resonance (234).

A similar interpretation may be applied to the observation of a number of authors (162, 224, 261, 263, 264), in working with crystals of anthracene, naphthacene, chrysene, and certain dyes, that absorption bands will appear when the exciting beam has its electric vector polarized parallel to the plane of the molecule, and that when the light is polarized normal to this plane a new band will arise.

---

[24] The acridine dyes show a large discrepancy and Lewis believed that what were calculated for x-bands were y-bands. That is, the oscillation corresponding to the lowest energy is vertical rather than horizontal.

E. x′-Bands

It has been shown that a molecule may have two optical axes and that excitation by light will produce an oscillation of an electron cloud along these two axes. Earlier, it was assumed that the whole system of quantized, mobile electrons moving in phase could be considered as a single oscillator analogous to a vibrating diatomic molecule. When such vibrations are harmonic, then the potential energy, V, will be proportional to the square of the displacement of what may be considered as the center of gravity of the electron cloud, x, and a plot of V against x will produce a parabola as, for example, in figure 17. The energy levels of the molecules may be indicated by evenly spaced lines parallel to the x-axis, whereby one lets the lowest represent the energy of the ground state and the next higher lines represent the energies of the succeeding excited states. The difference in energies of the first two lines will correspond to the main electronic absorption band of the molecule of frequency ν. When the molecule receives a higher excitation to the second excited state, resulting in an electronic oscillation of larger amplitude in the direction of greatest polarizability, one will observe a second absorption band of frequency ν', which Lewis and Bigeleisen have called an x'-band. Since the differences between energy levels are equal, the ratio of the two frequencies, ν'/ν, will be exactly 2; however, from selection rules, the probability of such a jump is zero. Therefore, the intensity, ϵ', of this second-order x-band will be zero and the ratio of the intensities of the two bands, ϵ'/ϵ, will be zero.

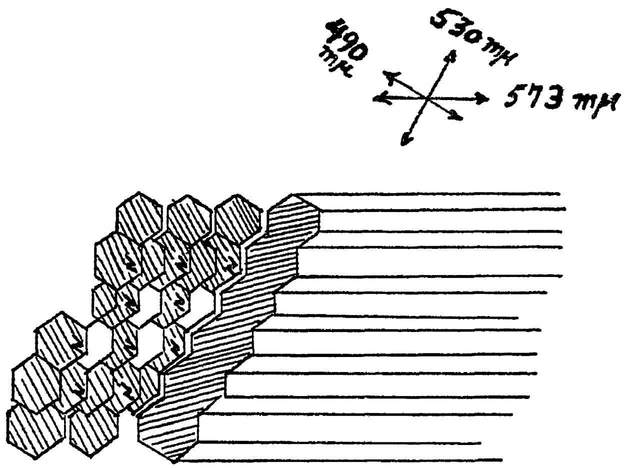


FIG. 16. Absorption and structure of the polymer of pseudoisocyanine. Redrawn from reference 32 through the courtesy of Prentice-Hall, Inc.

But then, if the electronic oscillations are anharmonic, the energy will rise less rapidly than the square of the displacement and the energy levels of the successive excited states will lie closer and closer together. In this case the ratio ν'/ν will be less than 2 and one might expect exceptions to the selection rules such that ϵ'/ϵ will be greater than zero. Lewis and Calvin (182) found in the spectra for the polyenes and carotenoids, and Lewis and Bigeleisen (178) observed in the

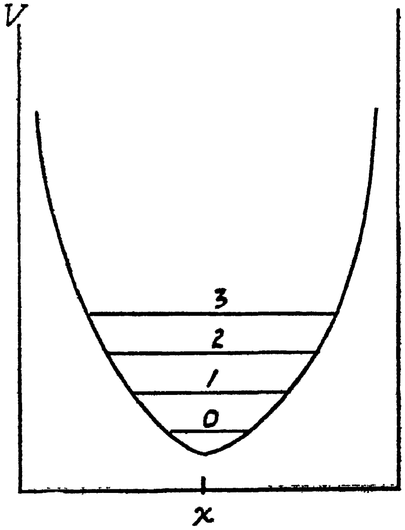


FIG. 17. Plot of potential energy, V, against electronic displacement, x

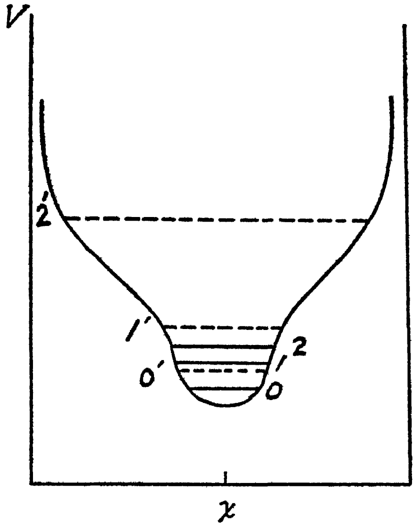


FIG. 18. Potential curve for electronic displacements in dye molecules

spectra of several types of dyes, a set of bands where the ratio of the frequencies, ν'/ν, was less than 2 and that of the intensities, ϵ'/ϵ, greater than zero. Nevertheless, as Lewis and Bigeleisen demonstrated, the ratio ν'/ν may be greater than 2.

Lewis and Bigeleisen constructed a potential diagram as in figure 18 where the levels 0, 1, 2, ... and 0′, 1′, 2′, . . correspond to the energy levels for two different substances. If the electronic oscillations are harmonic for certain amplitudes and become anharmonic for other amplitudes, the first two energy states of the molecule may occur in regions indicated by 1 and 2, where the difference between the first and second excited states is smaller than the difference between the ground and first excited states. This would result in the ratio of the frequencies of the x- and x'-bands, ν'/ν, being less than 2. On the other hand, if the energy states occur as indicated by the set of lines 0′, 1′, and 2′, where the transition from the first to the second excited state involves a greater amount of energy than the jump from the ground to the first excited state, the ratio of the frequencies, ν'/ν, will be greater than zero. The only factor which determines by which type of diagram the molecule will be represented is the amplitude of the electronic displacements relative to the dimensions of the molecule.

It is customary to write resonance formulas for unsaturated compounds, for instance, for a polyene

$$CH_2{=}CH{-}CH{=}CH_2 \qquad \overset{\mp}{C}H_2{-}CH{=}CH{-}\overset{\pm}{C}H_2$$

in which each atom holds its full complement of eight electrons in its valence orbit (excepting, of course, hydrogen atoms). Such structures actually represent the limit of electronic displacement and hence must correspond to the boundaries in the potential diagram of Lewis and Bigeleisen, where the energy is increasing very rapidly with increasing x. In this region the energy levels are spaced farther apart than in the lower area of the diagram. For a long molecule with a small λ_{max}, as, for instance, β-carotene or 1,14-diphenyltetradecaheptaene, with λ_{max} 480 mμ and 465 mμ, respectively (167), the electronic displacements must be small compared to the dimensions of the molecules, so that the first two excited states occur in the lower region of the diagram. But if λ_{max} is relatively large for a short molecule, as for the triphenylmethane dyes or cyanines, one may expect the electronic oscillations to be approaching the limiting resonance distances. Therefore, even the first few excited states are found in the upper portion of the potential diagram and the ratio, ν'/ν, will be greater than 2. The amplitude depends upon the polarizability of the molecule, being greater for those dyes with large λ_{max}. One can say, therefore, that in a series of similar compounds, as the values of λ_{max} of the x-bands increase, the ratio of the frequencies of the x- and x'-bands, ν'/ν, will increase, even to exceed 2, and simultaneously the ratio of the intensities, ϵ'/ϵ, will decrease.

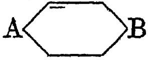
An excellent illustration to substantiate the existence of x'-bands in accordance with the above conditions was given by Kumler (169). He measured the spectra of eighteen compounds of the type AB, where A was an electron-donor such as the dialkylamino groups and B an electron-acceptor such as the NO_2, COOH, or SO_2NH_2 groups. His results are tabulated in table 7. Excluding the nitro compounds the trend agrees perfectly with the predictions of Lewis and Bigeleisen. Kumler explained the discrepancy in the case of the nitro compounds as due to the fusion of the nitro *partial* with the x'-band to make it unusually high and broad.

TABLE 7

Wave lengths and molar extinction coefficients of the absorption bands of some para-substituted aniline derivatives (Kumler (169))

COMPOUND IN 95 PER CENT ALCOHOL	λ_{max}	λ'_{max}	$\bar{\nu}$	$\bar{\nu}'$	ϵ	ϵ'	ν'/ν	ϵ'/ϵ
p-Nitrosodiethylaniline ...	428	275	23,300	36,400	31,100	5,470	1.56	0.176
p-Nitrosodimethylaniline...	423	273	23,600	36,600	29,400	5,750	1.55	0.195
p-Nitrodiethylaniline	400	236	25,000	42,400	21,550	8,850	1.70	0.412
p-Nitrodimethylaniline......	390	232	25,600	43,100	19,020	9,300	1.68	0.488
p-Nitroethylaniline	390	231	25,600	43,250	19,000	7,500	1.69	0.395
p-Nitromethylaniline...	386	230	25,900	43,400	18,430	7,470	1.68	0.405
p-Nitroaniline.......... ..	375	227	26,700	44,100	15,450	7,180	1.65	0.465
p-Diethylaminobenzaldehyde.	348	243	28,700	41,100	32,800	6,010	1.43	0.183
p-Dimethylaminobenzaldehyde...................	342	241	29,200	41,500	29,800	7,390	1.42	0.248
p-Dimethylaminoacetophenone......	337	239	29,700	41,800	25,600	6,340	1.41	0.248
p-Ethylaminoacetophenone..	332	238	30,100	42,000	25,900	6,030	1.40	0.233
p-Aminoacetophenone.......	317	233	31,500	42,900	20,100	6,750	1.36	0.336
p-Diethylaminobenzoic acid..	312	227	32,100	44,000	30,650	8,260	1.37	0.270
p-Dimethylaminobenzoic acid	308	227	32,400	44,000	25,400	7,450	1.36	0.293
p-Aminobenzoic acid.........	288	220	34,700	45,500	17,400	8,220	1.31	0.472
p-Diethylaminobenzenesulfonamide..................	280	213*	35,700	46,800	26,600	10,200	1.31	0.383
p-Dimethylaminobenzenesulfonamide..	276	211*	36,300	47,300	24,500	9,400	1.30	0.384
p-Aminobenzenesulfonamide..	262	204†	38,200	49,000	17,700		1.28	

* Kumler's estimate from curve.

† Kumler's estimate using Spekker and I. O. plates.

TABLE 8

Ultraviolet absorption characteristics of some p-disubstituted benzene derivatives

COMPOUND	λ_{max}	λ'_{max}	ϵ_{max}	ϵ'_{max}	ν'/ν	ϵ'/ϵ
p-Hydroxybenzoic acid.............	255	207.5	13,900	13,400	1.23	0.965
p-Anisic acid.......................	256.5	208	15,900	14,750	1.23	0.928
p-Nitroaniline cation..............	258	208	8,700	7,800	1.24	0.896
p-Aminobenzonitrile	270	212	19,800	13,800	1.27	0.698
p-Hydroxyacetophenone.......... ..	275	218.5	14,300	10,700	1.26	0.749
p-Methoxyacetophenone......	276.5	219.5	15,500	10,600	1.26	0.685
p-Nitrochlorobenzene......	280	217	10,300	7,150	1.29	0.694
p-Hydroxybenzaldehyde.	283.5	221	16,000	12,000	1.28	0.750
p-Aminobenzoic acid...	284	219.5	14,000	9,900	1.29	0.706
p-Nitrotoluene................ ...	285	217	9,250	6,700	1.31	0.725
p-Aminoacetophenone	311.5	231	17,100	6,950	1.35	0.406
p-Nitrophenol........	317.5	225.5	10,000	6,900	1.41	0.690
p-Hydroxyacetophenone anion.. ...	324.5	236.5	23,100	7,500	1.38	0.325
p-Hydroxybenzaldehyde anion.....	330	238	27,900	7,500	1.39	0.269
p-Nitroaniline................	381	226	13,500	6,700	1.69	0.497
p-Nitrophenol anion	402.5	226	19,200	6,500	1.78	0.338

Based on the criteria set up by Lewis and Bigeleisen, that in a series of similar compounds, as the values of λ_{max} of the x-bands increase, the ratio of the frequencies of the x'- and x-bands, ν'/ν, will increase and the ratio of the intensities, ϵ'/ϵ, will decrease, it seems that the two "primary" bands ($\epsilon < 2.6 \times 10^3$) (76a) for disubstituted benzenes are x- and x'-bands. Thus, for a number of compounds measured by Doub and Vandenbelt (76a), it is observed in table 8 that the trends in the ratios ν'/ν and ϵ'/ϵ are roughly as expected for x- and x'-bands. The agreement is not bad when one remembers that the exact values of λ_{max} are sometimes in doubt, because the absorption bands are broad and sometimes have very prominent shoulders.

X. SUMMARY

When a molecule absorbs light energy in the ultraviolet or visible region of the spectrum, electronic vibrations are set up within the molecule and it becomes excited to higher electronic vibrational levels. The difference in energies between the initial and final states determines the frequency of the absorbed light. A number of factors may influence the energy value of the initial and final states and thereby decrease or increase the energy difference between the two states. Thus it has been shown that the difference in energy, $E_1 - E_0$, between the ground state E_0 and the first excited state E_1 is diminished when there occurs resonance among structures which contribute chiefly to the excited state, thereby lowering the potential energy of the excited state, and also by steric hindrance existing in the ground state, thereby raising the potential energy of the ground state. Likewise, it has been shown that this energy difference is increased when the resonance occurs between structures which contribute primarily to the ground state, thus decreasing the energy of the ground state, and also by steric strain arising in the excited state which increases the potential energy of this state. With such an understanding, data from absorption spectra have been used to give information, sometimes unique, concerning the structure of an organic substance.

It has been shown further that the electronic vibrations produced by light excitation are oriented. Oscillations along the longest linear extension of conjugated multiple bonds cause the greatest stabilization of the excited state. This produces an absorption band of longer wave length than that arising from oscillations along any shorter conjugated system within the molecule.

A number of quantitative relationships between the wave length of the maximum absorption band and the structure of molecules have been presented. For instance, from absorption spectra one may determine the number of conjugated multiple bonds in a substance, the relative basic strengths of dyes, and the number of *trans* or *cis* ethylenic bonds in carotenoids.

Finally, through semiempirical approximation methods of quantum mechanics, the frequencies and intensities of light absorbed by simple molecules have been determined. Such calculations are of great value, because they give a large amount of information about the energies and electronic structures of organic molecules and their behavior under the influence of external fields.

The author is indebted to Mr. Theodore Austin, Instructor in Chemistry at Howard University, for drawing the figures in this article.

XI. REFERENCES[25]

(1) ADAMS, E. Q., AND ROSENSTEIN, L.: J. Am. Chem. Soc. **36**, 1452 (1914).
(2) AHMAD, S. S.: J. Indian Chem. Soc. **22**, 155 (1945).
(3) ALEXA, V.: Bul. Chim. Soc. Română Chim. [2] **1**, 77 (1939).
(4) ANSLOW, G. A.: J. Applied Phys. **16**, 41 (1945).
(5) ANSLOW, G. A., AND VAUGHN, E.: Phys. Rev. **62**, 298 (1942).
(6) ARENDS, B.: Ber. **64**, 1936 (1931).
(7) ARMSTRONG, H. E.: Proc. J. Chem. Soc. **1888**, 27.
(8) ASKEW, F. A.: J. Chem. Soc. **1935**, 509.
(9) BAEYER, A.: Ann. **354**, 152 (1907).
(10) BALY, E. C. C.: J. Chem. Soc. Trans. **89**, 489, 502, 514 (1906).
(11) BALY, E. C. C.: J. Soc. Chem. Ind. **34**, 393 (1915); J. Soc. Dyers Colourists **31**, 39 (1915).
(12) BALY, E. C. C.: Phil. Mag. **29**, 223 (1915); J. Chem. Soc. **107**, 1121 (1915).
(13) BANDOW, F.: Biochem. Z. **298**, 81 (1938).
(14) BASTRON, H., DAVIS, R. E., AND BUTZ, L. W.: J. Org. Chem. **8**, 515 (1943).
(15) BASTRON, H., DAVIS, R. E., AND BUTZ, L. W.: J. Am. Chem. Soc. **65**, 973 (1943).
(16) BATEMAN, L., AND KOCH, H. P.: J. Chem. Soc. **1945**, 216; Rubber Chem. Technol. **19**, 23 (1946).
(17) BATEMAN, L., AND KOCH, H. P.: Rubber Chem. Technol. **18**, 637 (1945).
(18) BATEMAN, L., AND KOCH, H. P.: J. Chem. Soc. **1944**, 600.
(19) BEILENSON, B., FISHER, N. I., AND HAMER, F. M.: Proc. Roy. Soc. (London) **A163**, 138 (1937).
(20) BENSON, S. W., AND KISTIAKOWSKY, G. B.: J. Am. Chem. Soc. **64**, 80 (1942).
(21) BERGMANN, W., AND HIRSCHMANN, F.: J. Org. Chem. **4**, 40 (1939).
(22) BERTON, A.: Ann. chim. **19**, 394 (1944); Chem. Abstracts **40**, 1733 (1946).
(23) BIELECKI, J., AND HENRI, V.: Ber. **47**, 1690 (1914).
(24) BIELECKI, J., AND HENRI, V.: Physik. Z. **14**, 516 (1913).
(25) BOWDEN, K., BRAUDE, E. A., JONES, E. R. H., AND WEEDON, B. C. L.: J. Chem. Soc. **1945**, 45, 948.
(26) BLOUT, E. R., AND EAGER, V. W.: J. Am. Chem. Soc. **67**, 1315 (1945).
(27) BLOUT, E. R., EAGER, V. W., AND GOFSTEIN, R. M.: J. Am. Chem. Soc. **68**, 1983 (1946).
(28) BLOUT, E. R., EAGER, V. W., AND SILVERMAN, D. C.: J. Am. Chem. Soc. **68**, 566 (1946).
(29) BLUMBERGER, J. S. P.: Rec. trav. chim. **63**, 127 (1944); Chem. Abstracts **39**, 2066 (1945).
(30) BOOKER, H., EVANS, L. K., AND GILLAM, A. E.: J. Chem. Soc. **1940**, 1453.
(31) BOWEN, E. J.: Ann. Repts. on Progress Chem. (Chem. Soc. London) **40**, 12 (1943).
(32) BRANCH, G. E. K., AND CALVIN, M.: *The Theory of Organic Chemistry*, 155 ff. Prentice-Hall, Inc., New York (1943).
(33) BRANCH, G. E. K., TOLBERT, B. M., AND LOWE, W.: J. Am. Chem. Soc. **67**, 1693 (1945).
(34) BRAUDE, E. A.: Ann. Repts. on Progress Chem. (Chem. Soc. London) **42**, 105 (1945).
(35) BRAUDE, E. A.: Nature **155**, 753 (1945).
(36) BRAUDE, E. A., AND JONES, E. R. H.: J. Chem. Soc. **1945**, 498.
(37) BRAUDE, E. A., JONES, E. R. H., AND ROSE, G. G.: J. Chem. Soc. **1947**, 1104.
(38) BRAUDE, E. A., JONES, E. R. H., AND STERN, E. S.: J. Chem. Soc. **1947**, 1087.
(39) BRODE, W. R.: *Major Instruments of Science and their Applications to Chemistry*, 69 ff. Interscience Publishers, Inc., New York (1945).
(40) BRODE, W. R.: J. Am. Chem. Soc. **51**, 1204 (1929).

---

[25] References do not necessarily indicate the author who first reported on the particular point, but rather the article in which the data can be found quite easily.

(41) Brode, W. R., and Herdle, L. E.: J. Org. Chem. **6**, 713 (1941).
(42) Brode, W. R., and Morris, R. J.: J. Org. Chem. **13**, 200 (1948).
(43) Brode, W. R., and Patterson, J. W.: J. Am. Chem. Soc. **63**, 3252 (1941).
(44) Brooker, L. G. S.: *Nuclear Chemistry and Theoretical Organic Chemistry*, 89 ff. Interscience Publishers, Inc., New York (1945).
(45) Brooker, L. G. S., and coworkers: Rev. Modern Phys. **14**, 275 (1942); J. Am. Chem. Soc. **67**, 1869, 1875, 1889 (1945).
(46) Brooker, L. G. S., and Sprague, R. H.: J. Am. Chem. Soc. **63**, 3214 (1941).
(47) Brooker, L. G. S., White, F. L., Sprague, R. H., Dent, S. G., Jr., and Van Zandt, G.: Chem. Revs. **41**, 325 (1947).
(48) Brooker, L. G. S., *et al.*: J. Am. Chem. Soc. **62**, 1116 (1940).
(49) Brown, W. G., and Reagan, H.: J. Am. Chem. Soc. **69**, 1032 (1947).
(50) Brunings, K. J., and Corwin, A. H.: J. Am. Chem. Soc. **64**, 593 (1942).
(51) Burawoy, A.: J. Chem. Soc. **1939**, 1177.
(52) Burawoy, A.: J. Chem. Soc. **1939**, 1177; Ber. **65**, 941, 947 (1932).
(53) Burawoy, A.: J. Chem. Soc. **1941**, 20.
(54) Burawoy, A.: Ber. **63**, 3155 (1930).
(55) Burawoy, A.: Ber. **64**, 462 (1931).
(56) Burr, G. O., and Miller, E. S.: Chem. Revs. **29**, 419 (1941).
(57) Bury, C. R.: J. Am. Chem. Soc. **57**, 2115 (1935).
(58) Calvin, M.: J. Org. Chem. **4**, 256 (1939).
(59) Calvin, M., and Wood, C. L.: J. Am. Chem. Soc. **62**, 3152 (1940).
(60) Campbell, N. R.: *Modern Electrical Theory*, 2nd edition. University Press, Cambridge (1913).
(61) Campbell, T. W., Linden, S., Godshalk, S., and Young, W. G.: J. Am. Chem. Soc. **69**, 880 (1947).
(62) Carr, E. P.: Chem. Revs. **41**, 293 (1947).
(63) Carr, E. P., and Burt, C. P.: J. Am. Chem. Soc. **40**, 1590 (1918).
(64) Carr, E. P., Pickett, L. W., and Stücklen, H.: Rev. Modern Phys. **14**, 260 (1942).
(65) Carr, E. P., and Stücklen, H.: J. Chem. Phys. **7**, 631 (1939).
(66) Chako, N. Q.: J. Chem. Phys. **2**, 644 (1934).
(67) Clar, E.: Ber. **69**, 607, 1671 (1936); **73**, 596 (1940).
(68) Conrad-Billroth, H.: Z. physik. Chem. **B33**, 133 (1936).
(69) Conrad-Billroth, H.: Z. physik. Chem. **B19**, 76 (1932); **B25**, 139 (1934).
(70) Conrad-Billroth, H., Forster, G., and Wagner, J.: Z. physik. Chem. **B35**, 343 (1937) and earlier publications in this series.
(71) Compton, C., and Bergmann, W.: J. Org. Chem. **12**, 363 (1947).
(72) Craig, D. P.: J. Chem. Soc. **1946**, 534.
(73) Crymble, C. R., *et al.*: J. Chem. Soc. **99**, 451, 1262 (1911).
(74) Dilthey, W.: Ber. **53**, 261 (1920); **64**, 1280 (1931) and previous papers.
(75) Dimroth, K.: Angew. Chem. **52**, 545 (1939).
(76) Discussion: Z. Elektrochem. **49**, 395 (1943).
(76a) Doub, L., and Vandenbelt, J. M.: J. Am. Chem. Soc. **69**, 2714 (1947).
(77) Dunicz, B. L.: J. Am. Chem. Soc. **63**, 2461 (1941).
(78) Dutt, S.: J. Chem. Soc. **1926**, 1171.
(79) Elion, G. B., Ide, W. S., and Hitchings, G. H.: J. Am. Chem. Soc. **68**, 2137 (1946).
(80) Euler, H. von, Karrer, P., Klussmann, E., and Morf, R.: Helv. Chim. Acta **15**, 502 (1932).
(81) Evans, L. K., and Gillam, A. E.: J. Chem. Soc. **1941**, 815.
(82) Evans, L. K., and Gillam, A. E.: J. Chem. Soc. **1943**, 565.
(83) Evans, L. K., and Gillam, A. E.: J. Chem. Soc. **1945**, 432.
(84) Ewing, G. W., and Steck, E. A.: J. Am. Chem. Soc. **68**, 2181 (1946).
(85) Ferguson, L. N., and Branch, G. E. K.: J. Am. Chem. Soc. **66**, 1467 (1944).
(86) Ferguson, L. N., and Goodwin, T. C.: Presented before the Division of Organic Chemistry at the 112th Meeting of the American Chemical Society, New York, September, 1947.

(87) Fieser, L. F., and Peckey, M. M.: J. Am. Chem. Soc. **68,** 2577 (1946).

(88) Fisher, N. I., and Hamer, F. M.: Proc. Roy. Soc. (London) **A154,** 703 (1936).

(89) Forster, G., Skrabal, R., and Wagner, J.: Z. Elektrochem. **43,** 290 (1937).

(90) Forster, G., and Wagner, J.: Z. physik. Chem. **B35,** 343 (1937).

(91) Forster, Th.: Z. physik. Chem. **B41,** 287 (1938); **B47,** 245 (1940); Z. Elektrochem. **45,** 549 (1939).

(92) Forster, Th.: Z. Elektrochem. **45,** 549 (1939).

(93) French, H. S., and Holden, M. E. T.: J. Am. Chem. Soc. **67,** 1239 (1945).

(94) Fromherz, H., Aumuller, W., and Strother, C. O.: Z. Elektrochem. **42,** 680 (1936).

(95) Funkhouser, J. A., and Brode, W. R.: J. Am. Chem. Soc. **56,** 2172 (1934).

(96) Goeppert-Mayer, M., and Sklar, A. L.: J. Chem. Phys. **6,** 245 (1938).

(97) Gillam, A. E., and Hey, D. H.: J. Chem. Soc. **1939,** 1170.

(98) Gillam, A. E., and West, T. F.: J. Chem. Soc. **1942,** 486.

(99) Graebe, C., and Liebermann, C.: Ber. **1,** 106 (1868).

(100) Grammaticakis, P.: Bull. soc. chim. **7,** 527 (1940).

(101) Hamner, W. F., and Matsen, F. A.: Presented before the Division of Physical and Inorganic Chemistry at the 112th Meeting of the American Chemical Society, New York, September, 1947.

(102) Hantzsch, A.: Ber. **43,** 82 (1910).

(103) Hantzsch, A.: Ber. **50,** 1413 (1917).

(104) Hanztsch, A., and Lifschitz, J.: Ber. **45,** 3011 (1912).

(105) Hartley, W. N.: J. Chem. Soc. Trans. **51,** 152 (1887).

(106) Hauser, K. W.: Z. tech. Physik **15,** 10 (1934).

(107) Hauser, K. W., Kuhn, R., Smakula, A., *et al.*: Z. physik. Chem. **B29,** 363, 371, 378, 384, 391, 417 (1935).

(108) Heilbron, I. M., Jones, E. R. H., and coworkers: J. Chem. Soc. **1943,** 261.

(109) Heilbron, I. M., Jones, E. R. H., and coworkers: J. Chem. Soc. **1942,** 727.

(110) Heilbron, I. M., Jones, E. R. H., and coworkers: J. Chem. Soc. **1944,** 134, 136, 140, 141, 144.

(111) Heilmeyer, L.: *Spectrophotometry in Medicine*, translated by A. Jordon and T. L. Tippell. Hilger, Ltd., London (1943).

(112) Heertjes, P. M., Bakker, R., and van Kerkhof, J. C.: Rec. trav. chim. **62,** 737, 745 (1943); Chem. Abstracts **39,** 67 (1945).

(112a) Henri, V.: *Études de photochimie.* Gauthier-Villars, Paris (1918).

(113) Henri, V., and Bergmann, E.: Nature **143,** 278 (1939).

(114) Henrich, F.: *Theories of Organic Chemistry*, pp. 382–478. John Wiley and Sons, Inc., New York (1922).

(115) Henrici, A.: Z. physik. Chem. **B47,** 93 (1940).

(116) Hartel, E.: Z. Elektrochem. **47,** 28 (1941).

(117) Hertel, E., and Siegel, U.: Z. physik. Chem. **B52,** 167 (1942).

(118) Hertel, E., and Schinzel, M.: Z. physik. Chem. **B48,** 289 (1941).

(119) Herzfeld, K. F.: Chem. Revs. **41,** 233 (1947).

(120) Herzfeld, K. F.: Proc. Am. Phil. Soc. **82,** 359 (1940).

(121) Herzfeld, K. F.: J. Chem. Phys. **10,** 508 (1942).

(122) Herzfeld, K. F., and Sklar, A. L.: Rev. Modern Phys. **14,** 294 (1942).

(123) Hewitt, J. T., and Mitchell, H. V.: J. Chem. Soc. Trans. **91,** 1251 (1907).

(124) Hillmer, A., and Schorning, P.: Z. physik. Chem. **A167,** 407 (1934).

(125) Hodgson, H. H., and Hathway, D. E.: Trans. Faraday Soc. **41,** 115 (1945).

(126) Hodgson, H. H., and Turner, H. S.: J. Soc. Dyers Colourists **59,** 218 (1943).

(127) Holmes, W. C.: Ind. Eng. Chem. **16,** 35 (1924).

(128) Hückel, E.: Z. Elektrochem. **43,** 752, 827 (1937).

(129) Hückel, W.: *Theoretische Grundlagen der organischen Chemie*, 2nd edition, p. 72. Akademische Verlagsgesellschaft, Leipzig (1935).

(130) Izmail'skiĭ, V. A., and Simonov, A. M.: J. Gen. Chem. (U.S.S.R.) **16,** 1659, 1667 (1946); Chem. Abstracts **41,** 6215 (1947).

(131) Jablonski, A.: Z. Physik **96**, 236 (1935).
(132) Jelley, E. E.: Nature **139**, 631 (1937).
(133) Jones, R. N.: Chem. Revs. **32**, 1 (1943).
(134) Jones, R. N.: Chem. Revs. **41**, 353 (1947).
(135) Jones, R. N.: J. Am. Chem. Soc. **65**, 1818 (1943).
(136) Jones, R. N.: J. Am. Chem. Soc. **67**, 2127 (1945).
(137) Jones, R. N.: J. Am. Chem. Soc. **63**, 1658 (1941).
(138) Jones, R. N.: J. Am. Chem. Soc. **63**, 313 (1941); **62**, 148 (1940).
(139) Jones, R. N.: J. Am. Chem. Soc. **67**, 2021 (1945).
(140) Jones, R. N.: Can. Chem. Process Ind. **28**, 497 (1944).
(141) Kaiser, E., and Koenig, V. L.: J. Am. Chem. Soc. **68**, 740 (1946).
(142) Karrer, P., and Ruegger, A.: Helv. Chim. Acta **23**, 955 (1940).
(143) Karrer, P., and Rutschmann, J.: Helv. Chim. Acta **25**, 1624 (1942).
(144) Karrer, P., and coworkers: Helv. Chim. Acta **28**, 1181, 1185 (1945).
(145) Katzenellenbogen, E. R., and Branch, G. E. K.: J. Am. Chem. Soc. **69**, 1978 (1947).
(146) Katzenellenbogen, E. R., and Branch, G. E. K.: J. Am. Chem. Soc. **69**, 1615 (1947).
(147) Kauffmann, H.: *Die Valenzlehre*, 344 ff., Enke, Stuttgart (1911); Ber. **46**, 3788 (1913).
(148) Kharasch, M. S., Nudenberg, W., and Sternfeld, E.: J. Am. Chem. Soc. **62**, 2034 (1940).
(149) Kharasch, M. S., and Tawney, P. O.: J. Am. Chem. Soc. **63**, 2308 (1941).
(150) Kharasch, M. S., and Tawney, P. O.: J. Am. Chem. Soc. **67**, 128 (1945).
(151) Kharkharov, A. A.: Trudy LKKhTI **1939**, No. 7, 157–87; Khim. Referat. Zhur. **1939**, No. 6, 96; Chem. Abstracts **34**, 4065 (1940).
(152) Kiss, A., and Auer, G.: Z. physik. Chem. **A189**, 344 (1941).
(152a) Klevens, H. B., and Platt, J. R.: J. Am. Chem. Soc. **69**, 3058 (1947).
(153) Klotz, I. M.: J. Chem. Education **22**, 328 (1945).
(154) Klotz, I. M.: Chem. Revs. **41**, 373 (1947).
(155) Klotz, I. M.: J. Am. Chem. Soc. **66**, 88 (1944).
(156) Konig, W.: J. prakt. Chem. [2] **112**, 1 (1926).
(157) Konig, W., and Meier, W.: J. prakt. Chem. **109**, 324 (1925).
(158) Konig, W., Schramek, W., and Rosch, B.: Ber. **61**, 2074 (1928).
(159) Kortum, G.: Z. physik. Chem. **B34**, 255 (1936).
(160) Kovner, M. A.: Compt. rend. acad. sci. U.R.S.S. **35**, 51 (1942); Chem. Abstracts **37**, 1652 (1943).
(161) Kovner, M. A.: Acta Physicochim. U.R.S.S. **19**, 385 (1935); Chem. Abstracts **39**, 3204 (1945).
(162) Krishnan, K. S., and Seshan, P. K.: Current Sci. **3**, 26 (1934); Z. Krist. **89**, 538 (1934); Proc. Indian Acad. Sci. **8A**, 487 (1938).
(163) Kuhn, R.: J. Chem. Soc. **1938**, 605.
(164) Kuhn, R.: Angew. Chem. **50**, 708 (1937).
(165) Kuhn, R., and Grundmann, C.: Ber. **70**, 1318 (1937).
(166) Kuhn, R., and Grundmann, C.: Ber. **71**, 442 (1938).
(167) Kuhn, R., and Winterstein, A.: Helv. Chim. Acta **12**, 899 (1929).
(168) Kuhn, R., and Winterstein, A.: Helv. Chim. Acta **11**, 144 (1928).
(169) Kumler, W. D.: J. Am. Chem. Soc. **68**, 1184 (1946).
(170) Kumler, W. D., and Strait, L. A.: J. Am. Chem. Soc. **65**, 2349 (1943).
(171) Kundt, A.: Ann. Physik Chem. **4**, 34 (1878).
(172) Kynch, G. J., and Penney, W. G.: Proc. Roy. Soc. (London) **A179**, 214 (1941).
(173) Lardy, G. C.: J. Chim. phys. **21**, 353 (1924).
(173a) Lemon, H. W.: J. Am. Chem. Soc. **69**, 2998 (1947).
(174) Lennard-Jones, J. E.: Proc. Roy. Soc. (London) **A158**, 280 (1937).
(175) Lewis, G. N.: Proc. Natl. Acad. Sci. U. S. **2**, 586 (1916).
(176) Lewis, G. N.: J. Am. Chem. Soc. **67**, 770 (1945).
(177) Lewis, G. N.: J. Am. Chem. Soc. **38**, 783 (1916); Proc. Natl. Acad. Sci. U. S. **2**, 586 (1916).

(178) Lewis, G. N., and Bigeleisen, J.: J. Am. Chem. Soc. **65,** 2107 (1943).

(179) Lewis, G. N., and Bigeleisen, J.: J. Am. Chem. Soc. **65,** 2102 (1943).

(180) Lewis, G. N., and Bigeleisen, J.: J. Am. Chem. Soc. **65,** 1144 (1943).

(181) Lewis, G. N., and Bigeleisen, J.: J. Am. Chem. Soc. **65,** 520 (1943).

(182) Lewis, G. N., and Calvin, M.: Chem. Revs. **25,** 273 (1939).

(183) Lewis, G. N., *et al.:* J. Am. Chem. Soc. **65,** 1150 (1943).

(184) Lewis, G. N., and Lipkin, D.: J. Am. Chem. Soc. **64,** 2801 (1942).

(185) Lewis, G. N., Lipkin, D., and Magel, T. T.: J. Am. Chem. Soc. **63,** 3005 (1941).

(186) Lewis, G. N., Magel, T. T., and Lipkin, D.: J. Am. Chem. Soc. **62,** 2973 (1940).

(187) Lewis, G. N., Magel, T. T., and Lipkin, D.: J. Am. Chem. Soc. **64,** 1774 (1942).

(188) Lewis, G. N., and Seaborg, G. T.: J. Am. Chem. Soc. **61,** 1886 (1939).

(189) Ley, H.: *Handbuch der Physik,* Vol. XXI, *Lichte und Materie,* 57 ff. J. Springer, Berlin (1929).

(190) Ley, H.: *Farbe und Konstitution bei organischen Verbindungen.* S. Hirzel, Leipzig (1911).

(191) Ley, H., *et al.:* Ber. **59,** 510 (1926); Ber. **67,** 501 (1934).

(192) Ley, H., and Spekker, H.: Z. wiss. Phot. **38,** 12 (1939).

(193) Lifschitz, J.: Z. wiss. Phot. **16,** 101 (1916).

(194) Lifschitz, J., and Rosenbohm, E.: Z. wiss. Phot. **19,** 198 (1920); **16,** 101 (1916).

(195) *Light Absorption and Constitution:* Z. Elektrochem. **47,** (G. Scheibe) 16, (M. Pestemer) 20, (E. Hertel) 28, (B. Eistert) 35, (G. Schwarzenbach) 40, (Th. Forster) 52, (G. Kortum) 55, (E. Wertz) 65, (G. Scheibe) 73 (1941).

(196) London, A.: J. Chem. Phys. **13,** 396 (1945).

(197) Lorenz, H., and Wizinger, R.: Helv. Chim. Acta **28,** 600 (1945).

(198) Luthy, A.: Z. physik. Chem. **107,** 285 (1923).

(199) Maccoll, A.: J. Chem. Soc. **1946,** 670.

(200) Maccoll, A.: Nature **157,** 695 (1946).

(200a) Mariella, R. P., Peterson, L. F., and Ferris, R. C.: J. Am. Chem. Soc. **70,** 1494 (1948).

(201) Martinez, J.: "Couleur et constitution chimique" in *Traitê de chimie organique,* sous la direction de V. Grignard, Secretaire General, Paul Baud, Tome II, Fascicule II, 653 (1936).

(202) Matsen, F. A., Robertson, W. W., and Chuoke, R. L.: Chem. Revs. **41,** 273 (1947).

(203) Mayer-Pitsch, E.: Z. Elektrochem. **49,** 368 (1943).

(204) Mayneord, W. V., and Roe, E. M. F.: Proc. Roy. Soc. (London) **A158,** 634 (1937).

(205) Meek, D. B.: J. Chem. Soc. Trans. **111,** 969 (1917).

(206) Menschick, W., Page, I. H., and Bossert, K.: Ann. **495,** 225 (1932).

(207) Merritt, E.: Phys. Rev. **28,** 684 (1926).

(208) Meunier, P.: Bull. soc. chim. **13,** 77 (1946).

(209) Mohler, H.: Helv. Chim. Acta **20,** 811 (1937).

(210) Moir, J.: Trans. Roy. Soc. S. Africa **17,** 51 (1929).

(211) Moir, J.: J. Chem. Soc. **119,** 1654 (1921); **121,** 1808 (1922); Trans. Roy. Soc. S. Africa **8,** 303 (1920).

(212) Morton, R. A.: Ann. Repts. on Progress Chem. (Chem. Soc. London) **38,** 7 (1941).

(213) Morton, R. A.: *The Application of Absorption Spectra to the Study of Vitamins, Hormones and Coenzymes,* 2nd edition. Hilger, Ltd., London (1942).

(214) Morton, R. A., and de Gouveia, A. J. A.: J. Chem. Soc. **1934,** 916.

(215) Morton, R. A., and Earlam, W. T.: J. Chem. Soc. **1941,** 159.

(216) Morton, R. A., Hassan, A., and Calloway, T. C.: J. Chem. Soc. **1934,** 883.

(217) Mulliken, R. S.: Chem. Revs. **41,** 201 (1947).

(218) Mulliken, R. S.: J. Chem. Phys. **7,** 339 (1939).

(219) Mulliken, R. S.: J. Chem. Phys. **7,** 20 (1939).

(220) Mulliken, R. S.: J. Chem. Phys. **7,** 364 (1939) and previous papers; Rev. Modern Phys. **14,** 265 (1942).

(221) Mulliken, R. S., and Rieke, C. A.: Repts. on Progress in Phys. **8**, 231, (1941).

(222) Mulliken, R. S., Riele, C. A. and Broxn, W. G.: J. Am. Chem. Soc. **63**, 41, (1941).

(223) Nietzki, R. H.: Verhandl. des Vereins zum Beforderung des Gewerbefleisses **58**, 231 (1879).

(224) Obreimov, I. V., and Prikhotko, A.: Physik Z. Sowjetunion **9**, 48 (1936); Chem. Abstracts **30**, 5502 (1936).

(225) O'Shaughnessy, M. T., and Rodebush, W. H.: J. Am. Chem. Soc. **62**, 2906 (1940).

(226) Pauling, L.: Proc. Natl. Acad. Sci. U. S. **25**, 577 (1939).

(227) Pestemer, M.: Z. Elektrochem. **47**, 20 (1941).

(228) Pestemer, M.: Z. Elektrochem. **49**, 361 (1943).

(229) Pestemer, M., and Gubitz, O.: Monatsh. **64**, 426 (1934).

(230) Pestemer, M., Langer, T., and Manchen, F.: Monatsh. **68**, 326 (1936).

(231) Pestemer, M., and Manchen, F.: Monatsh. **68**, 92 (1936).

(232) Pestemer, M., and Meyer-Pitsch, E.: Monatsh. **70**, 104 (1937).

(233) Pfeiffer, P.: Ann. **412**, 253 (1917).

(234) Pfeiffer, P.: *Organische Molekül-Verbindungen.* Enke, Stuttgart (1936).

(235) Pickett, L. W., Walter, G. F., and France, H.: J. Am. Chem. Soc. **58**, 2296 (1936).

(236) Piper, J. D., and Brode, W. R.: J. Am. Chem. Soc. **57**, 135 (1935).

(237) Plattner, Pl. A.: Helv. Chim. Acta **24**, 283E (1941); **26**, 905 (1943); **30**, 910 (1947).

(238) Price, C. C.: *Reactions at Carbon–Carbon Double Bonds*, pp. 9–12. Interscience Publishers, Inc., New York (1946).

(239) Price, W. C.: Ann. Repts. on Progress Chem. (Chem. Soc. London) **36**, 47 (1939).

(240) Price, W. C.: Chem. Revs. **41**, 257 (1947).

(241) Price, W. C., and Walsh, A. D.: Proc. Roy. Soc. (London) **A179**, 201 (1941).

(242) *Proceedings of the Seventh Summer Conference on Spectroscopy and its Applications.* John Wiley and Sons, Inc., New York (1940).

(243) Pullmann, A.: Compt. rend. **224**, 1354 (1947).

(244) Rabinowitch, E., and Epstein, L. F.: J. Am. Chem. Soc. **63**, 69 (1941).

(245) Rădulescu, D.: Ber. **64**, 2223 (1931).

(246) Rădulescu, D., and Alexa, V.: Ber. **64**, 2230 (1931).

(247) Rădulescu, D., and Georgescu, A.: Z. physik. Chem. **B5**, 189 (1929).

(248) Ramart-Lucas, P., and Amagat, P.: Bull. soc. chim. **51**, 965 (1932).

(249) Ramart-Lucas, P.: "Structure des molecules et spectres d'absorption in *Traité de chimie organique*, sous la direction de V. Grignard, Secretaire General, Paul Baud, Tome II, Fascicule I, 59 ff. (1936).

(250) Ramart-Lucas, P.: Bull. soc. chim. **10**, 13 (1943).

(251) Ramart-Lucas, P., and Hoch, J.: Bull. soc. chim. [5] **2**, 1376 (1935).

(252) Ramart-Lucas, P., and Hoch, J.: Bull. soc. chim. [5] **2**, 327 (1935).

(253) Reichstein, T., and Trivelli, G.: Helv. Chim. Acta **15**, 1074 (1932).

(254) Remick, A. E.: *Electronic Interpretations of Organic Chemistry*, p. 182. John Wiley and Sons, Inc., New York (1943).

(255) Remington, W. R.: J. Am. Chem. Soc. **67**, 1838 (1945).

(256) Rodebush, W. H.: Chem. Revs. **41**, 317 (1947).

(257) Rodebush, W. H., and Feldham, I.: J. Am. Chem. Soc. **68**, 896 (1946).

(257a) Rogers, M. T.: J. Am. Chem. Soc. **69**, 2544 (1947).

(258) Russell, R. G. and Coggeshall, N. D.: Chem. Ind. **58**, 586 (1946).

(259) Sandoval, A., and Zechmeister, L.: J. Am. Chem. Soc. **69**, 553 (1947).

(260) Sawyer, R. A.: *Experimental Spectroscopy.* Prentice-Hall, Inc., New York (1944).

(261) Scheibe, G.: Ber. **58**, 586 (1925).

(262) Scheibe, G.: Angew. Chem. **52**, 631 (1939).

(263) Scheibe, G., *et al.*: Z. Elektrochem. **49**, 372, 383 (1943).

(264) Scheibe, G., *et al.*: Kolloid-Z. **82**, 1 (1938); Naturwissenschaften **26**, 412 (1938); **27**, 499 (1939).

(265) Scheibe, G., and coworkers: Kolloid-Z. **82**, 1 (1938); Angew. Chem. **50**, 212 (1937).

(266) Scheibe, G., and Fromel, W.: *Hand- und Jahrbuch der chemischen Physik* **9**, (iii) 141 ff. Akademische Verlagsgesellschaft, Leipzig (1936).
(267) Scheibe, G., and Pummerer, R.: Ber. **60**, 2163 (1927).
(268) Schumann, S. C., and Aston, J. G.: J. Chem. Phys. **6**, 480, 485 (1938).
(269) Schwarzenbach, G.: Z. Elektrochem. **47**, 40 (1941).
(270) Schwarzenbach, G.: Helv. Chim. Acta **20**, 490 (1937); Z. Elektrochem. **47**, 40 (1941).
(271) Schwarzenbach, G., and coworkers: Helv. Chim. Acta **20**, 490, 498, 1591 (1937).
(272) Schwarzenbach, G., Lutz, K., and Felder, E.: Helv. Chim. Acta **27**, 576 (1944).
(273) Schwarzenbach, G., and Michaelis, L.: J. Am. Chem. Soc. **60**, 1667 (1938).
(274) Sheppard, S. E., *et al.*: J. Am. Chem. Soc. **66**, 1995 (1944) and previous papers in this series; Rev. Modern Phys. **14**, 303 (1942).
(275) Sheppard, S. E., Lambert, R. H., and Walker, R. D.: J. Chem. Phys. **9**, 96 (1941).
(276) Sherwood, D. W., and Calvin, M.: J. Am. Chem. Soc. **64**, 1350 (1942).
(277) Sklar, A. L.: Rev. Modern Phys. **14**, 232, 294 (1942); J. Chem. Phys. **10**, 521 (1942) and previous papers.
(278) Smakula, A.: Angew. Chem. **47**, 657 (1934).
(279) Snow, C. P., and Allsopp, C. B.: Trans. Faraday Soc. **30**, 93 (1934).
(280) Speas, W. E.: Phys. Rev. **31**, 569 (1928).
(281) Sponer, H.: Chem. Revs. **41**, 281 (1947), where additional references may be found.
(282) Sponer, H.: Rev. Modern Phys. **14**, 224 (1942); J. Chem. Phys. **7**, 207 (1939); **8**, 705 (1940).
(283) Stark, J., and Lipp, P.: Z. physik. Chem. **86**, 36 (1914).
(284) Stieglitz, J.: Proc. Natl. Acad. Sci. **9**, 303 (1923); J. Franklin Inst. **200**, 35 (1925).
(285) Stobbe, H., and Wildensee, F.: J. prakt. Chem. **115**, 163 (1927).
(286) Theilacker, W., and Ozegowski, W.: Ber. **73**, 898 (1940).
(287) Tolbert, B. M., and Branch, G. E. K.: J. Am. Chem. Soc. **69**, 1083 (1947).
(288) Tolbert, B. M., Branch, G. E. K., and Berlenbach, R. E.: J. Am. Chem. Soc. **67**, 887 (1945).
(289) Turnbull, N. H.: J. Chem. Soc. **1945**, 441.
(290) Vittum, P. W., and Brown, G. H.: J. Am. Chem. Soc. **69**, 152 (1947).
(291) Vittum, P. W., and Brown, G. H.: J. Am. Chem. Soc. **68**, 2235 (1946).
(292) Wagner-Jauregg, T., and Hippchen, H.: Ber. **76**, 694 (1943).
(293) Walker, O. J.: *Absorption Spectrophotometry and its Applications: Bibliography and Abstracts, 1932–1938.* Hilger, Ltd., London (1939).
(294) Walsh, A. D.: Trans. Faraday Soc. **43**, 158 (1947).
(295) Watson, E. R.: *Color in Relation to Chemical Constitution.* Longmans, Green and Company, London (1918).
(296) Wawilow, S. I.: Z. Physik **55**, 690 (1929).
(297) Weigert, F.: Physik. Z. **23**, 232 (1922).
(298) Wells, H. L.: Am. J. Sci. **3**, 417 (1922).
(299) Wheland, G. W.: *The Theory of Resonance*, p. 159. John Wiley and Sons, Inc., New York (1940).
(300) Wilds, A. L., *et al.*: J. Am. Chem. Soc. **69**, 1985 (1947).
(301) Williamson, B., and Rodebush, W. H.: J. Am. Chem. Soc. **63**, 3019 (1941).
(302) Willstatter, R., and students: Ber. **37**, 1494, 4605 (1904); **38**, 2244 (1905).
(303) Witt, O. N.: Ber. **9**, 522 (1876); **21**, 321 (1888).
(304) Wizinger, R. K.: *Organische Farbstoff.* Dümmlers Verlag, Berlin (1933).
(305) Wohl, A.: Bull. soc. chim. [5] **2**, 2135 (1935).
(306) Woodward, R. B.: J. Am. Chem. Soc. **64**, 72 (1942); see also reference 30.
(307) Woodward, R. B.: J. Am. Chem. Soc. **64**, 76 (1942).
(308) Zechmeister, L.: Chem. Revs. **34**, 267 (1944).
(309) Zechmeister, L., *et al.*: J. Am. Chem. Soc. **65**, 1940 (1943).
(310) Zechmeister, L., and Pinckard, J. H.: J. Am. Chem. Soc. **69**, 1930 (1947).
(311) Zechmeister, L., and Polgar, A.: J. Am. Chem. Soc. **66**, 137 (1944).
(312) Zechmeister, L., and Polgar, A.: J. Am. Chem. Soc. **65**, 1522 (1943).

THE CHEMISTRY OF THE PHTHALAZINES[1]

WYMAN R. VAUGHAN

Department of Chemistry, University of Michigan, Ann Arbor, Michigan

Received March 9, 1948

CONTENTS

I. Introduction 448
II. Preparation of phthalazines 448
III. Preparation of phthalazones 451
IV. Preparation of phthalhydrazides 463
V. Physical properties of phthalazines, phthalazones, and phthalhydrazides 466
VI. Reactions of the phthalazines 468
  A. Reduction 468
  B. Oxidation 469
  C. Ring cleavage 469
  D. Activity of halogen derivatives 470
  E. Alkylation 472
  F. Activity of the methyl group 473
  G. Salts and acyl derivatives 475
VII. Reactions of the phthalazones 475
  A. Reduction 475
  B. Reaction with phosphorus halides 475
  C. Phthalazonecarboxylic acids and their esters 476
  D. Hydrolysis 477
  E. Alkylation 478
  F. Acylation 478
  G. Amphoteric character 479
  H. Reaction with phosphorus pentasulfide 479
VIII. Pseudophthalazones 479
IX. Reactions of the phthalhydrazides 490
  A. Oxidation and reduction 490
  B. Resistance to substitution and hydrolysis 490
  C. Isomerization 490
  D. Reactions with phosphorus halides and phosphorus pentasulfide 492
  E. Acidic character 493
  F. Alkylation and acylation 493
  G. *N*-Substitution yielding acid derivatives 496
X. Chemiluminescence 496
  A. Nature of the phenomenon 496
  B. Promoters or accelerators 497
  C. Applications 498
  D. Luminescence spectra and absorption spectra 498
  E. Effect of substituents on chemiluminescence 499
  F. Lack of luminescence in five-membered-ring isomers 499
  G. Chemifluorescence 499
  H. Mechanism of chemiluminescence 499

---

[1] The name phthalazine was first used by Liebermann (92).

I. Rôle of the accelerator 503
J. Quenching effect of excess alkali 503
XI. Uses of phthalazines, phthalazones, and phthalhydrazides 504
XII. References 504

I. INTRODUCTION

Although the chemical literature contains many articles reporting research involving the preparation and properties of the phthalazines and their oxygenated derivatives, the phthalazones and phthalhydrazides, there is no one paper or series of papers to which one can turn for a survey of the field. Much of the published data is of an incomplete nature, since the compounds in question have frequently arisen incidental to other research; but despite this often subsidiary character, the questions of structure and reactivity raised by all three classes of substances are of more than passing interest. Relatively few investigators have devoted any major effort to the elucidation of such problems; and while the work of such men as Gabriel, Curtius, Rowe, Rădulescu, Drew, and others has been very comprehensive, within narrow limits, no comprehensive study has been published for the series as a whole. The majority of investigators have been content to prepare a number of related compounds, record their properties, and pass on to new work. Those studies dealing with the influences governing formation of the azine ring are tantalizingly incomplete, and studies of mechanism are all but non-existent.

It is the purpose of the present paper to summarize the more important phases of synthesis and reaction in phthalazine chemistry without making an exhaustive catalogue of all of the reported syntheses and reactions, to indicate, insofar as possible on the basis of existing data, reasonable mechanisms for certain of the more important reactions, and to call attention to a few of the more important deficiencies in experimental data in various phases of phthalazine chemistry.

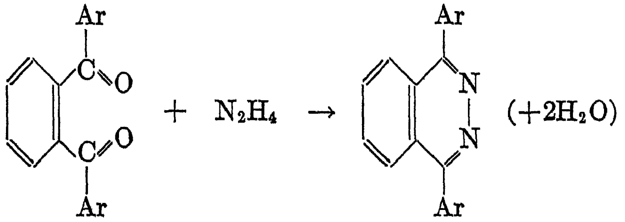
The nomenclature, insofar as possible, will be based upon the current usage of *Chemical Abstracts*, but the reader is warned that many systems are in use, some authors even varying within a single series of papers. Consequently names and formulas presented in the present paper may at first glance seem to be rather at variance with those in the original papers.

Since the larger portion of purely chemical research in the field concerns itself with synthesis, this phase will be treated first, with the physical properties and chemical behavior following in that order. In the phthalhydrazide series, unlike the phthalazine and phthalazone series, the syntheses have almost invariably been carried out for the purpose of studying a particular phthalhydrazide. Generally speaking, such syntheses are of a conventional nature, and relatively little space has been devoted to a study of the formation of phthalhydrazides. Once the phthalhydrazides have been formed, however, their chemistry has been the subject of much investigation; hence an effort will be made to evaluate the various studies of isomerism and chemiluminescence encountered in this field.

II. PREPARATION OF PHTHALAZINES

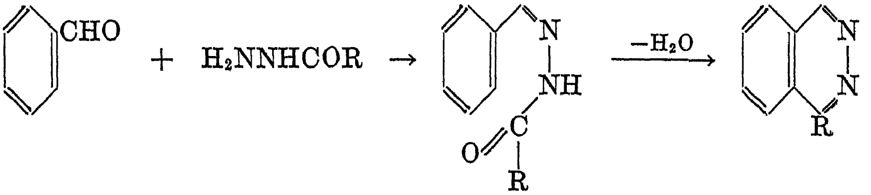
The preparation of simple phthalazines has been carried out according to two general methods. Transformation of phthalazones or phthalhydrazides in their lactim forms into halogenated phthalazines (by means of phosphorus halides) with subsequent reduction, or by replacement of the active halogen with a suitable reagent (e.g., alkali alkoxides), constitutes the most generally used method, and these reactions will be discussed under the sections treating the chemical behavior of phthalazones and phthalhydrazides.

However, direct formation of the azine ring, which constitutes the other general method, has occasionally been used. This method may be subdivided into three types of reaction: (*1*) the reaction of an *o*-diaroylbenzene derivative with hydrazine (10, 11, 25, 39, 69, 70, 151, 154),



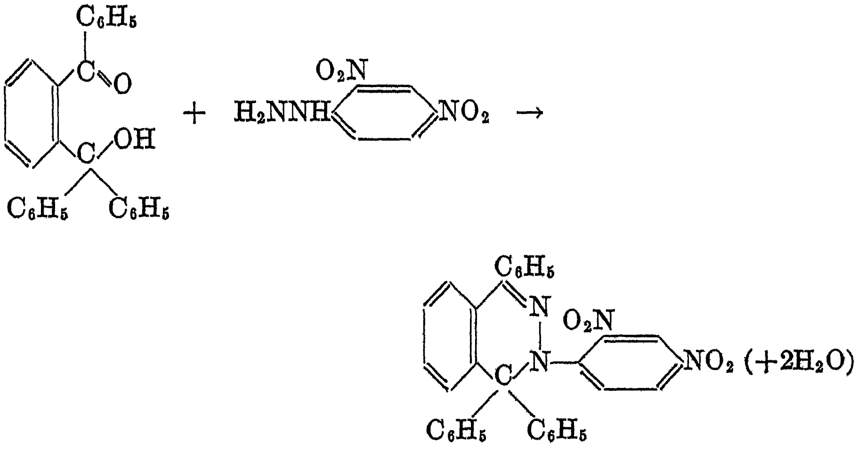
(1)

(*2*) the reaction of a hydrazide with an appropriately substituted aromatic aldehyde, followed by cyclodehydration of the acylhydrazone (1, 2),



(2)

and (*3*) the reaction of an *o*-benzoyltriphenylcarbinol (or its tautomeric cyclic ketal) with a hydrazine derivative to yield a 1,2-dihydrophthalazine derivative (155):



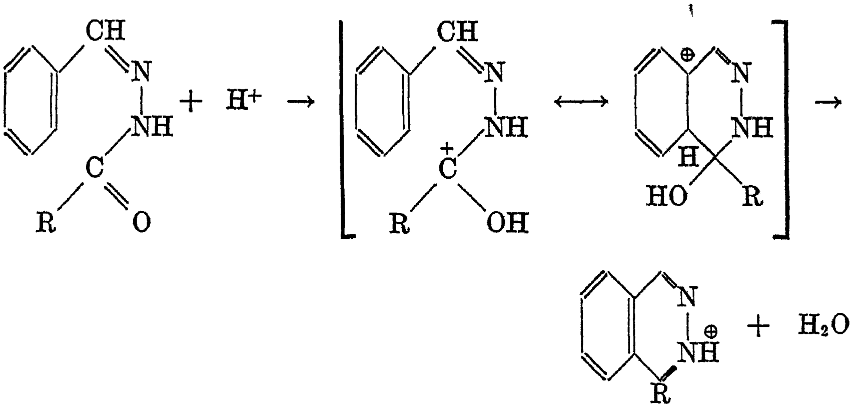
(3)

In reaction 1 an aqueous solution of hydrazine is added to a suitable solution of the diketone in alcohol (25, 70, 154), acetic acid (10, 11), or even pyridine (25, 151). The yields in general are good. In passing it should be noted that the *o*-diketone has occasionally been obtained from a β,β'-benzofuran by oxidation, using sodium dichromate in acetic acid solution (70, 154).

Reaction 2 has been used very successfully with both benzhydrazide and phenylacethydrazide in reaction with a variety of aromatic aldehydes (1, 2), but it was observed that where the aldehyde carried a substituent *only* in the meta position, cyclization seemed to be inhibited, regardless of the character of the substituent, for both *m*-nitro- and *m*-methoxy-benzaldehyde failed to yield phthalazines. However, both veratraldehyde and piperonal gave satisfactory yields of phthalazines under the same conditions. Consequently the results with *m*-methoxybenzaldehyde would appear to be anomalous, but no investigation of possible reasons for the anomaly or the extent to which other groups produce the same effect has been published.

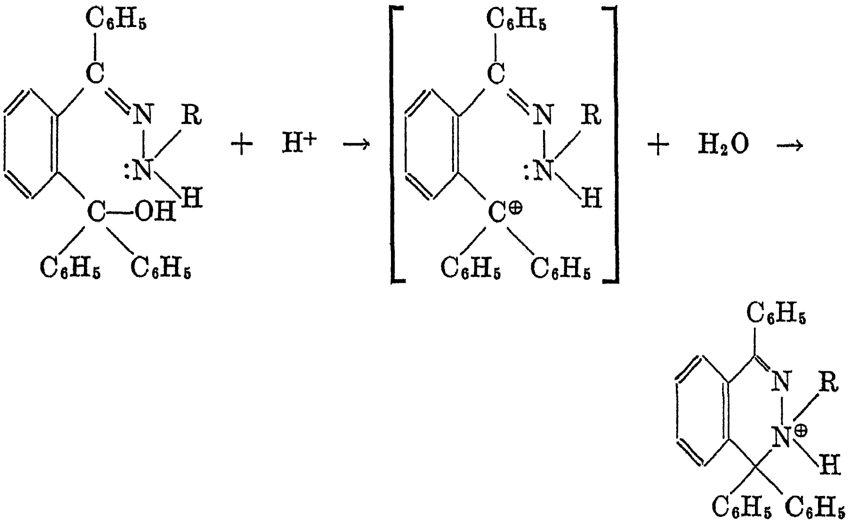
Reaction 3, yielding a 1,2-dihydrophthalazine, is a less common type of reaction and was observed to take place in alcohol solution containing concentrated hydrochloric acid. Such a solution of the keto-carbinol was treated with 2,4-dinitrophenylhydrazine, and somewhat over 50 per cent of the *N*-substituted dihydrophthalazine was obtained (155).

The mechanism for formation of the simple phthalazines directly from an *o*-diketo compound (equation 1) offers no unusual points for consideration, since it is essentially a double condensation of hydrazine with the two carbonyl groups. However, reaction 2 is rather more complex. The initial process is the usual condensation of a hydrazide with a carbonyl group, but the second step is the more significant one and merits more investigation of the forces promoting or hindering it. The actual cyclization is acid catalyzed and may be regarded as a typical cyclodehydration (16):



(4)

The reaction yielding a 1,2-dihydrophthalazine (equation 3) is likewise acid catalyzed, and it also resembles the formation of certain phthalazone derivatives (equations 7d and 15):



(5)

III. PREPARATION OF PHTHALAZONES

Far more abundant literature exists describing the preparation of phthalazones, both with and without substituents on the nitrogen and on C^4. There are many examples of synthesis recorded for all types of compounds, and they may be classified under three major headings: straightforward reactions yielding simple phthalazones (equation 6), less usual modifications of these reactions yielding similar products (equations 7), and somewhat more unusual reactions (represented by equations 8 through 10) (see table 1).

The conditions under which the most common phthalazone synthesis (equation 6) has been carried out vary from simply warming a mixture of an *o*-acylbenzoic acid and the appropriate hydrazine derivative in aqueous solution through the use of alcoholic solvents or acetic acid to the extreme situation where the *o*-acylbenzoic acid was heated to a high temperature with phenylhydrazine alone. In general the use of an aqueous medium has been given preference, since the reaction product is usually relatively insoluble in cold water, and the yields are usually very good. Use of simple esters of *o*-acylbenzoic acids as starting materials is comparatively infrequent (5, 97), but enol-lactones have often proven quite satisfactory (15, 147, 190, 192).

The use of substances which may be considered as related to enol-lactones has also been of some interest: equation 7c represents the usual course of such a reaction, while there is evidence that certain reactions of the type represented by equation 6 can proceed through an intermediate stage of similar character (102, 103) (*cf.* equation 12, below). The transformation represented by equation 7c has been effected either with or without solvents, but the transformation of the product of reaction 12 into a phthalazone is effected by treatment with an aqueous acid (equation 14, below). While there is no actual record of a reaction such as that represented by equation 12 occurring with *o*-ketobenzoic acids, the isolation of an intermediate which is subsequently transformed into a phthalazone

TABLE 1

Preparation of phthalazones

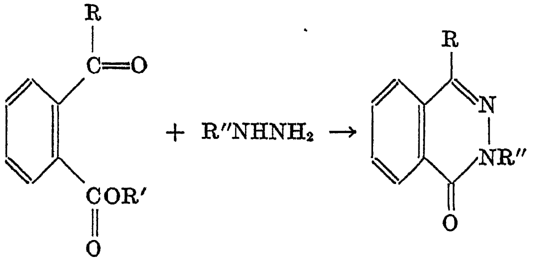
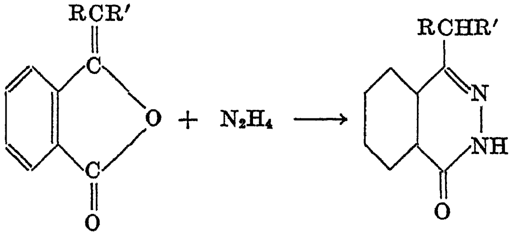
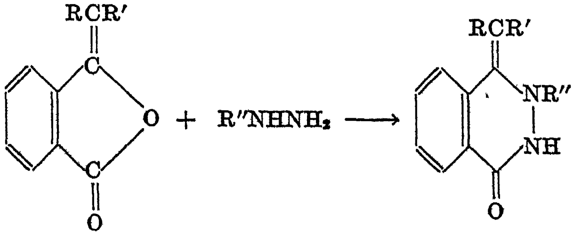
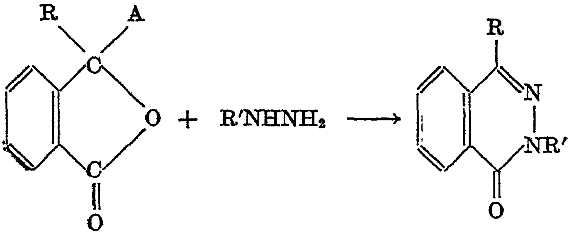
EQUATION	REFERENCES
(6)  R = H, alkyl, aryl, COOR′ R′ = H, alkyl R″ = H, aryl, NH$_2$CO	(5, 7, 14, 15, 20 27, 34, 38, 48, 50, 55, 56, 58, 59, 60, 61, 62, 67, 77, 84, 90, 93, 97, 102, 106, 107, 108, 110, 112, 117, 125, 152, 153, 180, 182, 190)
(7a)  (*cf.* equation 19) R = styryl R′ = COOH (lost in product), H	(15)
R, R′ = *o*, *o*′-diphenyl	(192)
R = phenyl R′ = H	(20)
(7b)  (*cf.* equation 10) R = acetyl R′ = carbethoxy R″ = phenyl	(147)
(7c)  R = H, alkyl, aryl R′ = H, alkyl, aryl A = H, halogen, amino, arylamino, OR	(99, 172, 180, 190)

TABLE 1—*Continued*

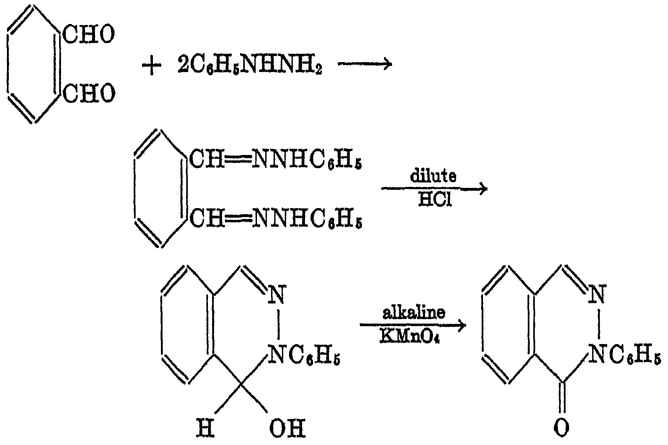
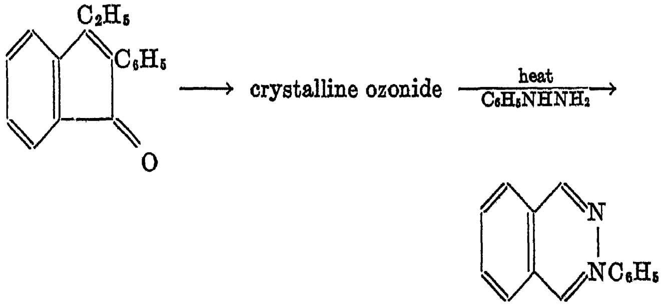
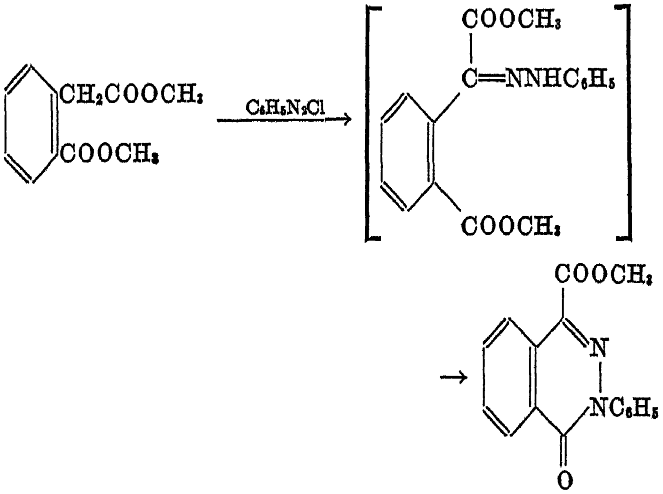
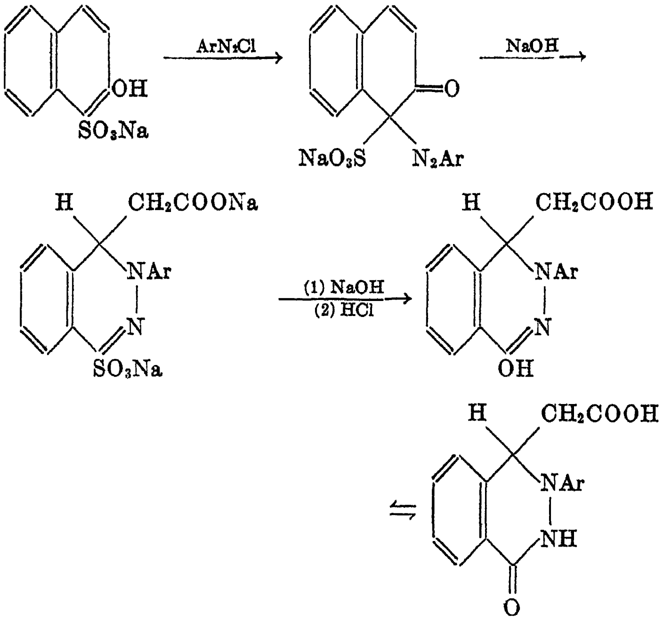
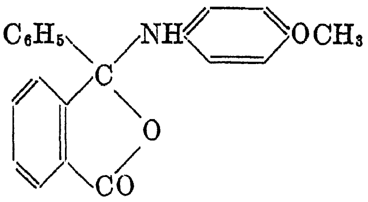
EQUATION	REFERENCES
(7d)  CHO CHO + 2C₆H₅NHNH₂ CH=NNHC₆H₅ CH=NNHC₆H₅ dilute HCl N NC₆H₅ H OH alkaline KMnO₄ N NC₆H₅ O (*cf.* equation 3)	(173)
(8)  C₂H₅ C₆H₅ O crystalline ozonide heat C₆H₅NHNH₂ N NC₆H₅	(54)
(9)  CH₂COOCH₃ COOCH₃ C₆H₅N₂Cl COOCH₃ C=NNHC₆H₅ COOCH₃ COOCH₃ N NC₆H₅ O	(13, 37)

TABLE 1—*Concluded*

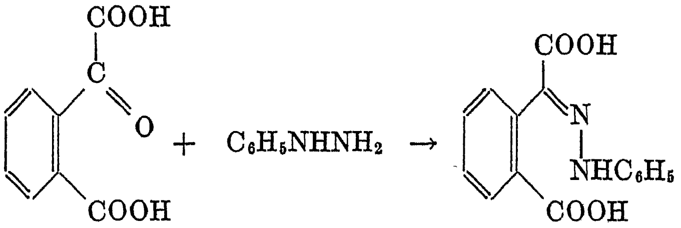
EQUATION	REFERENCES
(10)  (*cf.* equation 7b)	(127–145)

by treatment with acid strongly suggests that all reactions of the type represented by equation 6 are subject to acid catalysis (7, 27, 146), especially since many such reactions seem to proceed smoothly in acetic acid solution (15, 117); and there are frequent references to the transformation of a hydrazone to the corresponding phthalazone in the presence of acetic acid or of strong mineral acids (50, 90, 108, 146, 153). However, ring closure also occurs in weakly alkaline solution as recorded by Gabriel and others (58, 61, 180); so acid catalysis is not indispensable, though perhaps it should be stated that a high pH value for a solution retards or inhibits cyclization altogether (179). Further evidence of the lack of necessity for acid catalysis is to be found in the formation of phthalazones directly from phenylhydrazine and the appropriate *o*-acylbenzoic acid (56, 84, 97).

The isolation of hydrazones as intermediates in phthalazone formation has been reported in many places where a substituted hydrazine has been employed, and this raises a question as to the structure of these hydrazones: Are they true hydrazones, or are they pseudohydrazones formed as in equation 12? The actual isolation of pseudohydrazones (phthalidohydrazines) is recorded only twice (102, 103) by authors who were particularly interested in obtaining such substances, and to this end they worked under rather unusual conditions in their attempts to obviate direct phthalazone formation. The possibility, indeed the ease of formation of a substance of similar structure from *o*-benzoylbenzoic acid and *p*-anisidine (99),

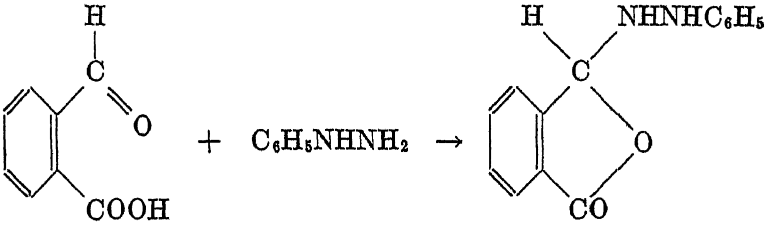


raises the question of whether or not the hydrazones which have been isolated (27, 38, 50, 90, 93, 192) from reactions of hydrazine or its derivatives with *o*-acylbenzoic acids may not actually be pseudohydrazones. Either hydrazone or pseudohydrazone can be converted to the phthalazone structure by treatment with aqueous acids; hence there is reason to reëxamine the results recorded in these studies. The ability of a substance to form a pseudohydrazone is undoubtedly a function of the various groups close to the carbonyl group, and one might venture to predict on the basis of such evidence as is available that groups which exert a $+I$ (electron-attracting) effect seem to favor ordinary hydrazone formation:



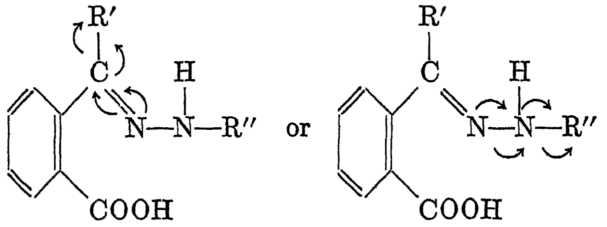
(11)

while those exerting a $-I$ (electron-repelling) effect or a zero inductive effect (H) tend to favor the formation of a pseudohydrazone:



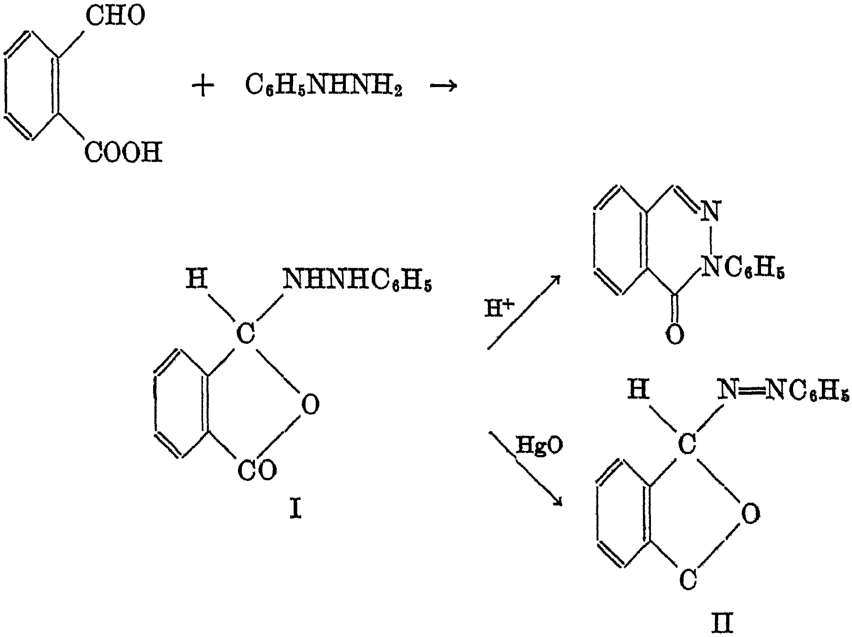
(12)

It might be further suggested that the presence of so strong a $+I$ group as NO_2 in the original aromatic ring or in the hydrazine molecule would tend to favor normal hydrazone formation by a transmitted $+I$ effect. In either of the latter two conditions the over-all result would be a tendency to disperse or delocalize the effect of the lone pair of electrons on the doubly bound nitrogen atom of the hydrazone, thus rendering it a less attractive site for the transfer of an acidic proton (i.e., its basicity is reduced):



or both.

The pseudohydrazone structure was first seriously considered to have an independent existence by Mitter and Sen (102, 103), who offered as proof of its existence the relative ease of oxidation of the product of reaction between phthalaldehydic acid and phenylhydrazine. As illustrated in equation 13 the pseudohydrazone (phthalidophenylhydrazine) may be oxidized to phenylazophthalide (II):

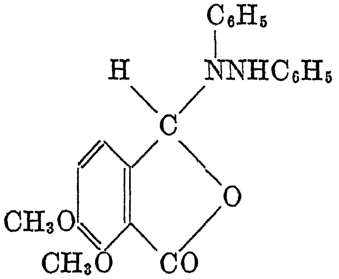


(13)

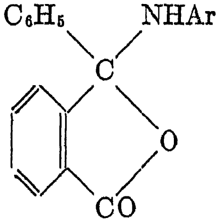
whereas such an oxidation would not be readily possible in the isomeric *o*-phthalaldehydic acid phenylhydrazone without the tautomeric shift necessary to produce the lactone-like pseudohydrazone.

Substance I is described as being canary-yellow and readily soluble in aqueous ammonia or aqueous *sodium bicarbonate*, which of course would also be true of the tautomeric hydrazone. The authors make no effort to distinguish between the reactions of I and those of the true hydrazone except as regards susceptibility to oxidation. The azo compound (II) obtained from I proves to be insoluble in aqueous sodium bicarbonate and therefore must possess the cyclic structure indicated.

As already noted, it is quite evident that I is a tautomeric form of the true hydrazone structure and would be expected to be stable only in neutral or slightly acidic solutions, the conditions governing its stability being the inductive effects aforementioned and the pH of any given solution. Hence it is to be supposed that in a strongly alkaline solution the hydrazone structure will exist exclusively. Very early evidence for a closely related structure is to be found in the work of Tust (175), who obtained a *non-acidic* substance from opianic acid, an *N,N'*-diphenylhydrazine to which he assigned the structure,



and similar investigation of the reaction of *o*-benzoylbenzoic acid with aromatic amines led Meyer to propose a pseudoanilide structure (98):



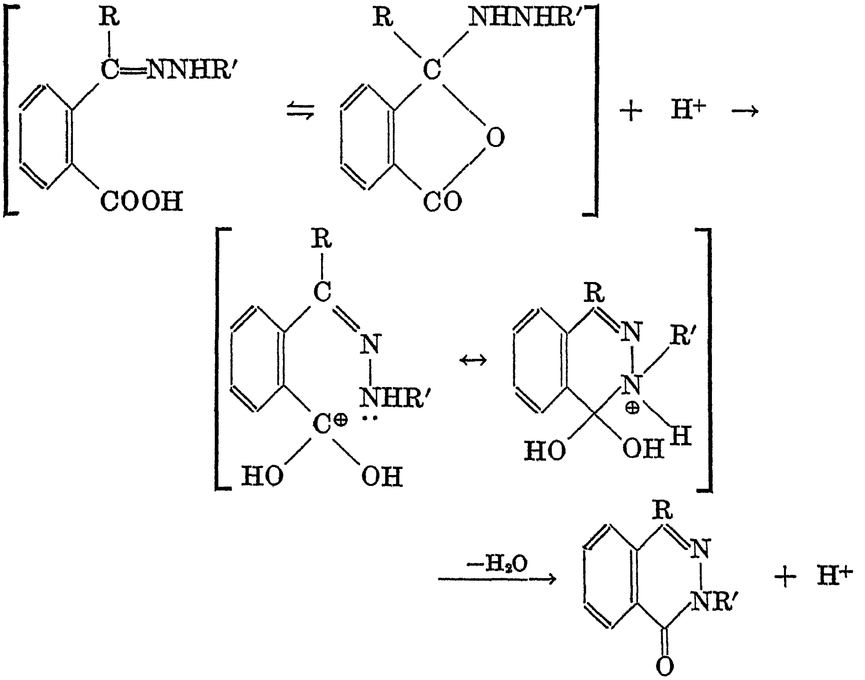
Meyer's compounds are titratable, but certain of them show a definite lag in reactivity with alkali. An extension of Meyer's work along the lines initiated by Mitter and Sen would doubtless prove quite fruitful as a means of studying the relative stabilities of pseudohydrazones.

Support for the influence of substituents on the nature of the hydrazine derivative is to be found in the work of the latter authors, who state that they could not obtain any identifiable products from attempts to oxidize the phenylhydrazine derivative from phthalonic acid. Here, of course, the α-carboxyl group exerts a +*I* effect.

The same influences which operate to stabilize the true hydrazone structure might also be expected to inhibit or retard cyclization to a phthalazone (equation 14). There is a certain amount of data to support this hypothesis, and indeed the resistance toward cyclization (stability of the hydrazones) has been investigated by Rowe and his collaborators (133). Their findings show that +*I* groups in ortho or para (or both) positions in the arylhydrazine molecule definitely retard cyclization of the hydrazone formed with an *o*-acylbenzoic acid, while −*I* groups attached to the carbonyl carbon atom promote cyclization. The $+I$ effect is also observed in the meta position, but to a lesser degree.

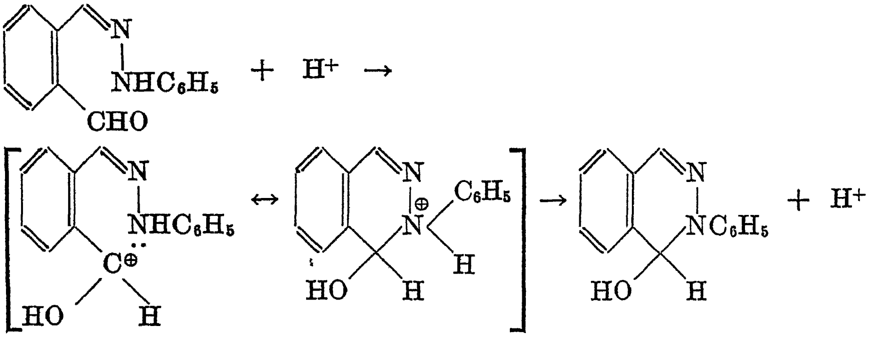
Rowe himself does not attempt to classify or correlate inductive effects in his studies, but he does make reference to an ortho effect which operates where there are ortho groups in the hydrazine molecule. There is no reason to doubt the existence of this effect, but it seems only reasonable that the inductive (and/or resonance) effects are of considerably more significance, especially since arylhydrazines containing $-I$ groups form hydrazones which appear to cyclize with extraordinary ease (128, 131, 133).

A mechanism which would appear to account for the cyclization of either form (pseudo or normal) of the hydrazone into a phthalazone derivative is indicated by the following equation (*cf.* 71):



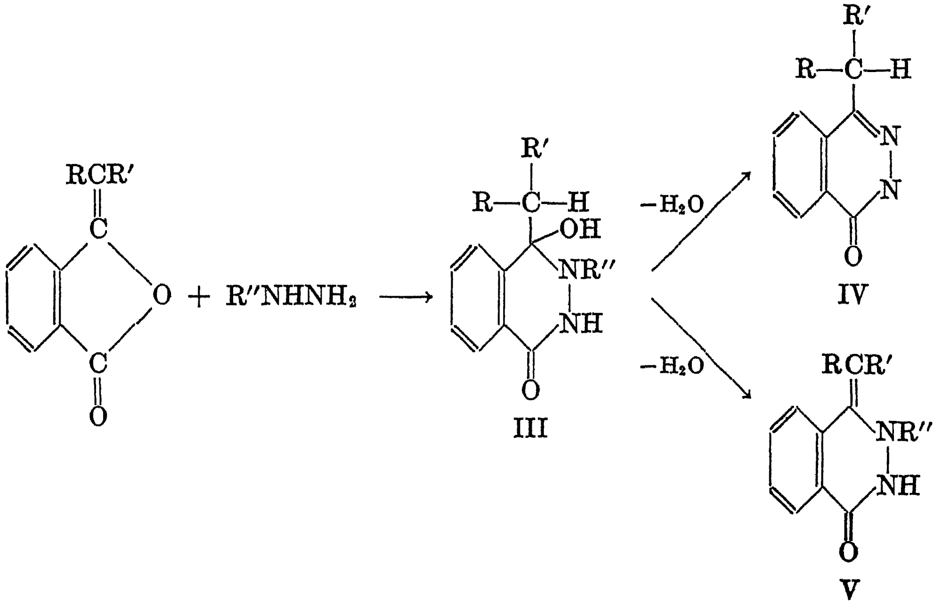
(14)

A similar mechanism may be written for equation 7d, assuming prior hydrolysis of one of the phenylhydrazone groups:



(15)

The mechanism for reactions 7a and 7b is identical with equation 14, the difference in final structures arising from the fact that the enol-lactones must first be opened with a hydrazine molecule. The resulting hydrazide then cyclizes to the keto group as in equation 14 to yield a substance (III) which is capable of loss of water in two ways, depending on its structure: where R″ = H, the usual phthalazone (IV) is formed, but where R″ ≠ H, a 3,4-dihydrophthalazone derivative results (V).

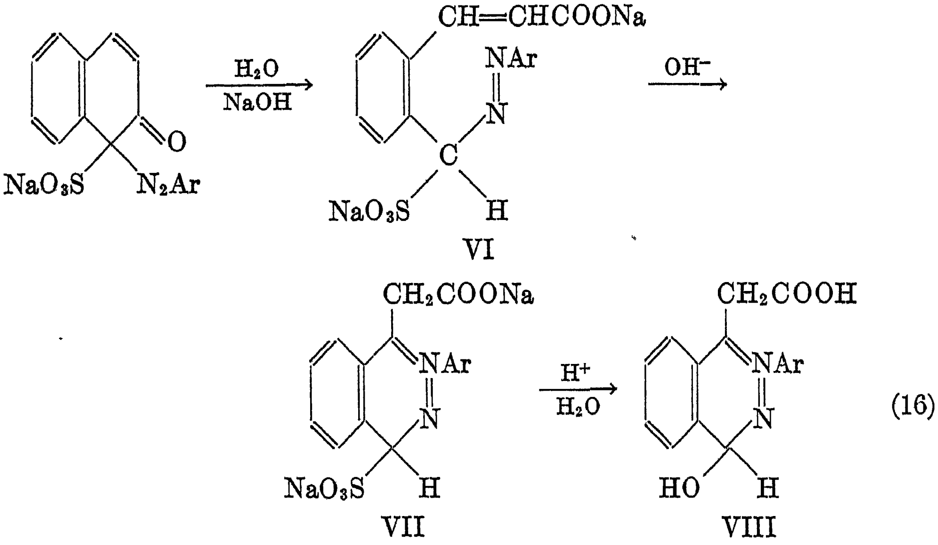


The lactone structure in equation 7c is transformed into a hydrazone structure by opening the lactone ring with hydrazine, followed by spontaneous loss of HA; in equation 9 the hydrazone structure arises from condensation of the diazonium salt with the active methylene group of a homophthalic ester. In both equations 7c and 9 subsequent cyclization to the phthalazine structure then follows the same course illustrated in equation 14.

Only reactions 8 and 10 remain to be elucidated. The former is evidently unique and requires additional data as to the nature of the other reaction products before any conclusions as to mechanism can be reached, but the latter has been studied in some detail and merits rather careful attention.

The extensive investigations of Rowe and his collaborators (127–145) into the preparations of phthalazine derivatives are concerned chiefly with studying the conditions for their particular method of synthesis and with the chemical behavior of their unusual phthalazones, once they have been formed. The actual preparation is illustrated by equation 10. The nature of the diazonium salt has been widely varied: in the initial reaction Ar = 4-nitrophenyl, 2-chloro-4-nitrophenyl, 2-bromo-4-nitrophenyl, 2-methyl-4-nitrophenyl, 2,6-dichloro-4-nitrophenyl, 2,6-dibromo-4-nitrophenyl; 2-nitrophenyl, 2-nitro-4-chlorophenyl, 2-nitro-4-methylphenyl; 3-nitrophenyl; 4-benzeneazophenyl, 4-(4′-nitrobenzene)azophenyl.

The preparation of the azo compound from sodium 2-naphtholsulfonate and the requisite diazonium salt presents no unusual problem (137), but the subsequent cleavage with sodium hydroxide to a benzene derivative was misinterpreted for some time as a simple hydrolytic cleavage followed by direct cyclization:



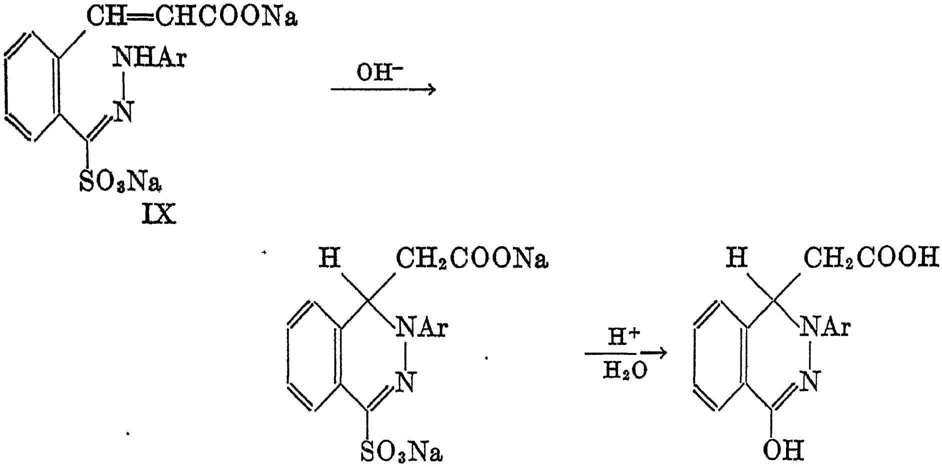
VI

VII

VIII

(16)

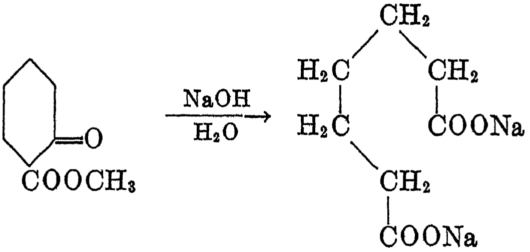
The authors adopted this course for the reaction, since they were for some time unable to prepare "*N*-methyl ethers" from the final product (VIII). However, in view of later findings in which the previously inaccessible *N*-methyl derivatives were prepared from VIII (Ar = 2-nitrophenyl or 2-nitro-4-chlorophenyl), the structures of the intermediates were altered and VI, VII, and VIII were replaced by IX, X, and XI, respectively, the latter in particular being structurally more reasonable.



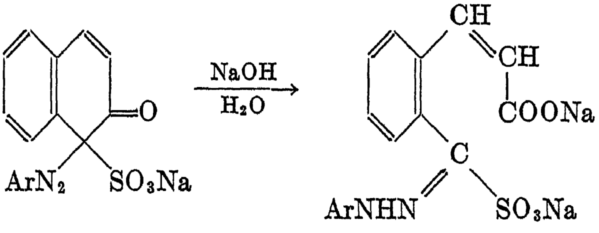
IX

X

The formation of IX from the naphthalene derivative possibly proceeds according to the usual mode of hydrolysis for a carbonyl compound in which the α-carbon carries groups exerting a strong +*I* effect. For example, compare the following well-known reaction,

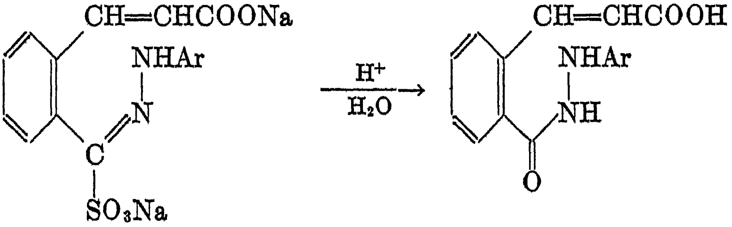


with



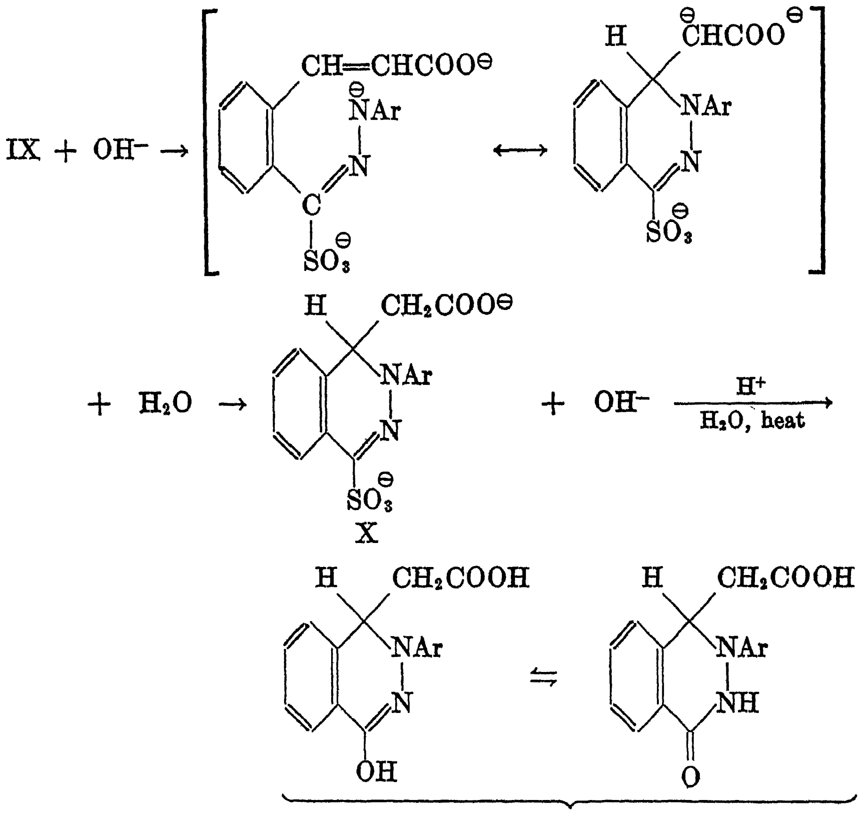
IX

Then follows a tautomeric rearrangement to the hydrazone structure (equation 17). Where there is an *o*-nitro group in the original diazonium salt the intermediate open-chain compounds have been isolated and examined, and upon hydrolysis in acid solution a hydrazide (XII) is obtained which could best have been formed from IX rather than from VI (which would yield a quite different and unstable product) (128):



IX XII

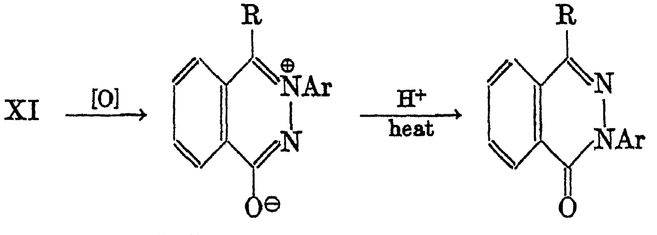
For the actual cyclization of the open-chain structure (IX) the position of the mobile proton is not important, since the anion of IX alone is required, and indeed cyclization usually occurs spontaneously in the alkaline medium required to transform the naphthalene derivative into IX:



XI

(17)

The function of the alkaline medium is of course to produce the anion (resonating structure shown in brackets). The carbanion structure (attached to C^4) is then represented as removing a proton from water to yield X. Subsequent acidic hydrolysis of X then yields the structure XI, which exists in two tautomeric forms. The structure of XI is proven indirectly by further transformations:



XIII: $R = CH_3$ XV: $R = CH_3$
XIV: $R = H$ XVI: $R = H$

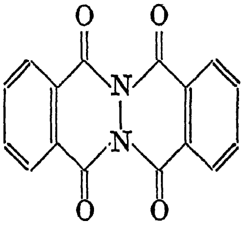
(18)

Treatment of XI with cold acidic dichromate yields XIII, while refluxing with dilute sulfuric acid yields XIV. Both XIII and XIV are readily shown to be isomeric rather than identical with the more common forms XV and XVI, which may be synthesized by unequivocal methods. Furthermore, XIII may be transformed into XV and XIV into XVI by heating with 1.2 *N* hydrochloric acid in a sealed tube at 170–190°C. for about 6 hr. Consequently the reactions represented by equations 10 and 18 may be used for the preparation of the isomeric 2- and 3-arylphthalazones. The mechanism and conditions for the transformations shown in equation 18 will be discussed under the chemical behavior of the pseudophthalazones.

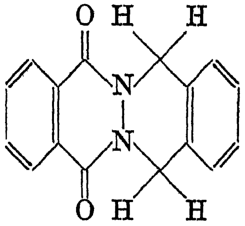
IV. PREPARATION OF PHTHALHYDRAZIDES

The cyclic hydrazides of *o*-phthalic acid and its derivatives have in general been prepared from derivatives of the corresponding phthalic acids (e.g., the acids themselves, esters, anhydrides, imides, etc.) and an appropriately substituted hydrazine derivative. The formation of isomeric phthalimidines will be considered below.

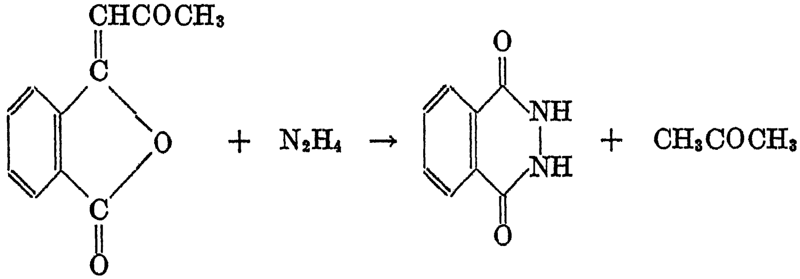
In addition to the usual bicyclic hydrazides a few polycyclic structures have been synthesized by treating a phthalhydrazide with *o*-phthaloyl chloride derivatives or with α,α'-dichloro-*o*-xylenes (45, 75), the respective products having the general structures:



and



Two unconventional reactions yield phthalhydrazides:[2] one is essentially the cleavage of a β-keto enol-lactone by means of hydrazine (21):



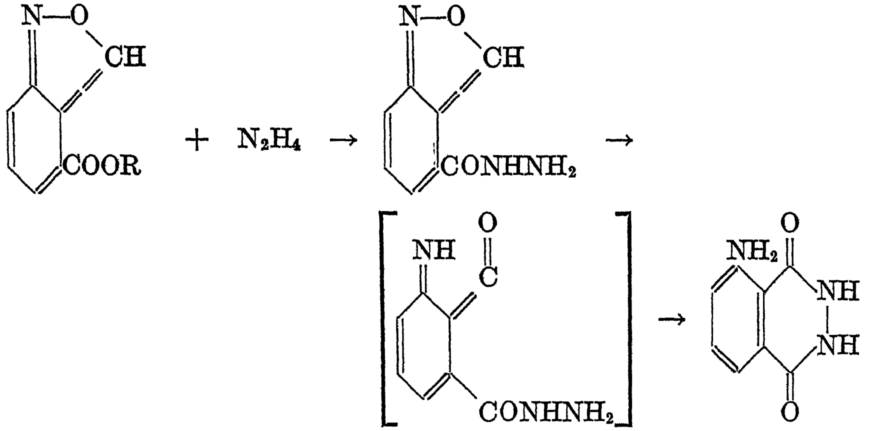
(19)

(*cf.* equation 7a)

while the other is a reaction of an *o*-carboxybenzisoxazole (or its ester) with hydrazine (66):

---

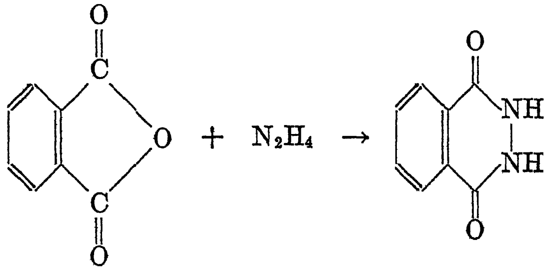
[2] A number of unusual reactions yielding phthalhydrazides have been carried out by Rowe and his collaborators, but discussion of these will be reserved for consideration with the reactions of the pseudophthalazones.



(20)

The intermediate hydrazide has actually been isolated when methylhydrazine has been used in place of hydrazine itself.

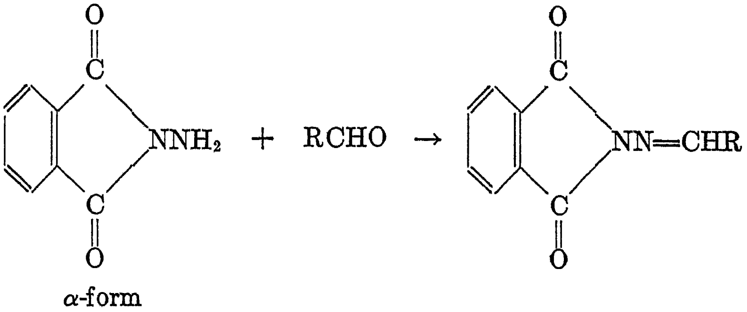
As with the synthesis of the simple phthalazines from hydrazine and an *o*-diacylbenzene there is nothing of an unusual nature which merits consideration in the formation of a phthalhydrazide directly from an *o*-phthalic acid or one of its derivatives; all that is involved is the well-known reaction of an ammonia derivative with an acid derivative, followed by a second similar reaction with the other end of the hydrazine molecule (29):



(21)

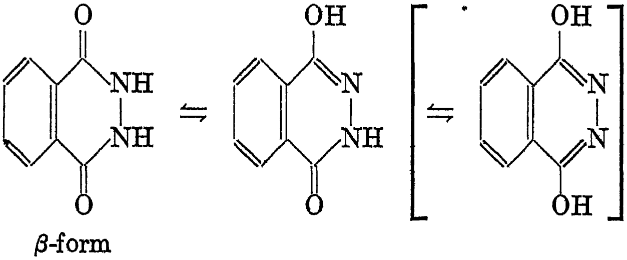
Curtius (30) states that no dihydrazide of *o*-phthalic acid can be obtained (*cf.* 156); however, it was very early observed that an isomeric non-acidic structure could also be prepared from *o*-phthalic acid derivatives and the derivatives of hydrazine (29, 79, 111). In the earlier investigations it appeared that phthalhydrazide or *N*-phenylphthalhydrazide was formed in the presence of two equivalents of the hydrazine derivative while the non-acidic isomer, *N*-aminophthalimide, was formed preferentially in the presence of one equivalent of the hydrazine derivative. Later investigations seemed to bear out this early observation, and the studies of Drew in this field will be considered subsequently.

Some confusion appears to have arisen in the early work in the field of phthalhydrazide synthesis, since the isomeric *N*-aminophthalimides (phthalylhydrazides) exist in polymorphic forms (47, 183), but the proof of structure offered by Rădulescu (118–122), which followed Sidgwick's study of isomerism, tautomerism, and polymorphism in this series (157), established the true relationship between *N*-aminophthalimides and the isomeric phthalhydrazides. The structure proof is based upon the chief characteristic of the two isomeric structures. The so-called α-form (*N*-aminophthalimide) reacts with aldehydes, as would any hydrazide with a similarly free amino group:



(*cf.* equation 49)

while the β-form (phthalhydrazide) is soluble in alkali and forms stable salts with metals such as silver by virtue of a tautomeric lactim structure:



Furthermore, the phthalhydrazide structure yields (from the dilactim) both mono- and di-chlorophthalazines with phosphorus pentachloride; with phosphorus pentasulfide a dimercaptan is formed (equation 52) (122). It was also shown conclusively that even the *N*-phenyl derivative of the α-form could be transformed into the β-form by means of strongly basic catalysis (sodium ethoxide in alcohol) (24), while heat alone was sufficient for *N*-aminophthalimide itself (45). The extreme conditions for this isomerization are quite in accord with Rădulescu's contention that the α-form vigorously resists hydrolysis and therefore this structure cannot represent the acid isomer, which depends for its acidity upon a readily reversible hydrolysis, as had been suggested by Rothenburg (183). Absorption spectra of the *N*-phenyl derivatives of the two isomers show marked differences (8).

As mentioned above, the question of which type of substance (*N*-aminophthalimide or phthalhydrazide) is formed under a given set of conditions has been investigated by Drew and his collaborators, and a certain amount of data has been accumulated. The investigations are not especially complete, since they were mainly incidental to the investigation of the phenomenon of chemiluminescence which was being studied by Drew. It is the opinion of the present writer that insufficient experimental data is available to warrant offering any conclusions as to mechanisms or group influences. Undoubtedly something more than simple steric effects is responsible for the differences observed, and probably both resonance and inductive effects must be considered. However, a summary of the findings of Drew and his collaborators is presented herewith for consideration (45).

Certain groups in the phthalic acid ring were found to promote five-membered-ring (*N*-aminophthalimide) formation, while others were found to promote six-membered-ring (phthalhydrazide) formation, and still others promoted the formation of either five-membered or six-membered rings—the former when only one equivalent of hydrazine was used, the latter when two equivalents of hydrazine were present. This latter class comprises 3-aminophthalimide, 3-chlorophthalimide, and 3,6-dichlorophthalic anhydride. Those substances yielding only the six-membered-ring structure are 4-aminophthalimide, 3-hydroxyphthalimide, 3- or 4-nitrophthalic anhydride, 4,5-dichlorophthalimide, and 4,5-dichlorophthalic anhydride. Finally, two substances yield only the five-membered-ring structure: 3,6-dichlorophthalimide and 3,4,5,6-tetrachlorophthalic anhydride.[3] Attention is called to the fact that those phthalic acids which form anhydrides with difficulty (4,5-dichloro) yield the six-membered-ring structure exclusively, while those forming an anhydride more readily (3,6-dichloro) can yield either the five-membered or the six-membered ring. Drew further suggests a situation analogous to the Mills–Nixon effect (52, 101).

It was further observed that when there was a hydrazide group ortho to the nitro group of 3-nitrophthalic acid, simple heating invariably favored formation of a six-membered ring; but if the hydrazide was meta to the nitro group a five-membered ring resulted regardless of the state of the ortho carboxyl, indeed, even though the latter also carried a hydrazide. Finally, the use of methylhydrazine favored formation of the six-membered-ring structure.

As will be noted the evidence is incomplete, and the effect of groups so vastly different in their influences as nitro and amino in the *same positions* is so similar as to be incapable of simple explanation in conventional terms. The subject merits further study, especially along lines which would make possible, independently of each other insofar as feasible, an examination of the resonance, inductive, and steric factors influencing the course of these reactions.

Information as to the ease of phthalhydrazide formation where an arylhydrazine is used is more definite; and as might be expected, the ease of cyclization shows a definite relationship to the nature of the substituents in the arylhydrazine nucleus, $+I$ groups retarding and $-I$ groups promoting (*cf.* page 457) cyclization in the phthalazone series (131, 133).

V. PHYSICAL PROPERTIES OF PHTHALAZINES, PHTHALAZONES, AND PHTHALHYDRAZIDES

The physical properties of the phthalazines are related to those of the corresponding naphthalenes very much as the properties of the pyridazines are related to those of benzene derivatives. Morton (104) refers to the effect of the benzo group upon the melting point of a substance, stating that its presence results in a 78°C. rise. It would perhaps be more accurate to permit rather more of a range than does Morton, since between pyridine and isoquinoline there is only a 65°C. increase (−46°C. to +23°C.), while between pyridazine and phthalazine there is a difference of 98°C. (−8°C. to +90°C.).

---

[3] Phelps (113) and Rădulescu and Alexa (120) believed that they had obtained a six-membered hydrazide ring from tetrachlorophthalic acid and even reported derivatives and salts, but Drew states categorically that they did not have 5,6,7,8-tetrachlorophthalhydrazide (45).

The variation in melting points within the two series—benzene structure and naphthalene structure—follows the same pattern, though in the latter series the differences are exaggerated: benzene +5.5°C., pyridine −46°C., pyridazine −8°C.; naphthalene 80°C., isoquinoline 23°C., phthalazine 90°C. The initial drop from the homocyclic structure to the heterocyclic system in the benzene series is −47.5°C., while in the naphthalene series it is −57°C.; and the subsequent rise in the benzene series is +34°C., while in the naphthalene series it is +67°C., bringing the melting point of the final member above that of the first member.

The boiling points in the two series show more regularity, and here the naphthalene series shows a more gradual increase: benzene 80°C., pyridine 115°C., pyridazine 208°C.; naphthalene 218°C., isoquinoline 243°C., phthalazine 316°C. In the benzene series the increases are respectively +35°C. and +93°C., while in the naphthalene series the corresponding increases are +25°C. and +73°C.

It is beyond the scope of this article to consider reasons for the relatively small abnormalities encountered in the melting point series, and since there is little physical data such as absorption spectra, dipole moments, etc. recorded in the literature, any detailed discussion of physical properties must await further experimental exploration along physicochemical lines.

Although no systematic record of the effect of substitution upon the melting points of the phthalazines is available, certain generalities may be adduced from a consideration of available data. The parent substances—phthalazine, phthalazone (1-hydroxyphthalazine, 1-keto-1,2-dihydrophthalazine), and phthalhydrazide (1,4-dihydroxyphthalazine, 1,4-diketo-1,2,3,4-tetrahydrophthalazine)—are all white crystalline substances with melting points of 90°C. (62, 110), 183–184°C. (61, 110, 184), and 341–344°C. (cor.) (45), respectively. The presence of various substituents (with the exception of carboxyl) in the hetero-ring usually lowers the melting point of the parent substance, especially if the substituent is attached to nitrogen. Large aromatic nuclei attached to C^4 of phthalazone raise the melting point.

In phthalazine and phthalazone substitution in the carbocyclic ring usually raises the melting point; but in phthalhydrazide there appears to be no general conformity as regards effect of substitution in the carbocyclic ring, though there is a tendency of monosubstitution (even of the nitro group!) to lower the melting point slightly, while disubstitution raises it.

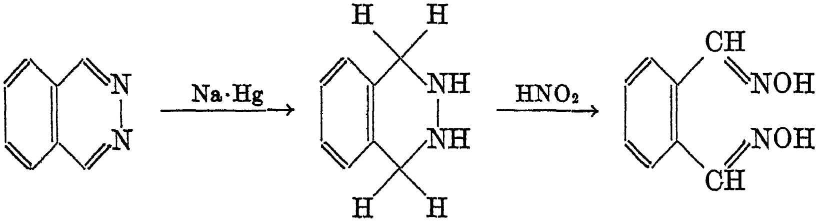
In the absence of additional chromophoric groups or of strong auxochromic groups, the phthalazines, phthalazones, and phthalhydrazides are white or occasionally yellow crystalline substances. The absorption spectra of the latter have received some attention (8, 19, 51, 64, 120, 196), chiefly because of certain unusual phenomena observable in various members of the series. Otherwise no systematic study of the physical characteristics of these substances is available. The reader is referred to the work of Padoa (109) for certain cryoscopic data relating to phthalazine and quinoxaline in hydrocarbon solvents.

VI. REACTIONS OF THE PHTHALAZINES

The reactions of phthalazine and its non-oxygenated substitution products are readily collected into relatively few general classes.

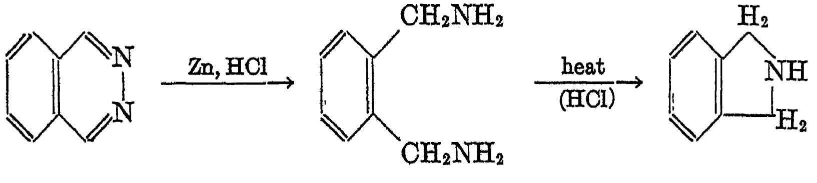
A. Reduction

First of all the action of reducing agents is of interest: phthalazine itself upon treatment with sodium amalgam yields tetrahydrophthalazine, which may be transformed into the dioxime of *o*-phthalaldehyde by reaction with nitrous acid, or which reduces Fehling's solution and regenerates phthalazine (62, 94).



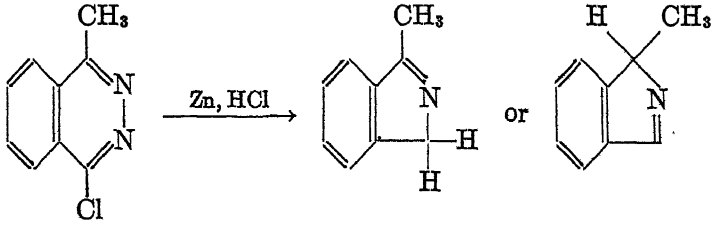
(22)

On treatment with zinc and hydrochloric acid, however, phthalazine yields α,α'-diamino-*o*-xylene, which upon warming with hydrochloric acid is transformed into dihydroisoindole (59, 61, 62), reactions of which are reported by Fränkel (55) in a paper in which the latter substance is prepared from a phthalazone derivative



(23)

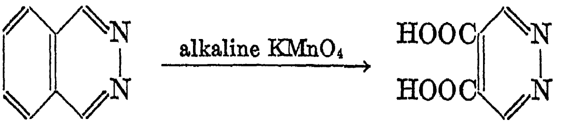
by reduction. Where a C^1-alkyl-C^4-halogenophthalazine is used in place of phthalazine itself, reaction 23 yields an isoindole (59, 61), which would appear to be the only source of the free isoindole structure (*cf.* 158).



(24)

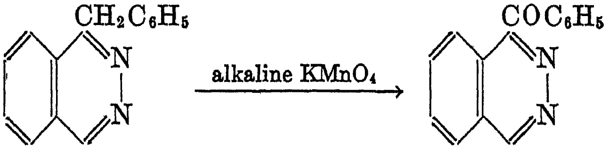
B. Oxidation

The action of oxidizing agents on the phthalazine system is analogous to their action on quinolines: i.e., the carbocyclic ring is broken (57) and a pyridazine is formed.



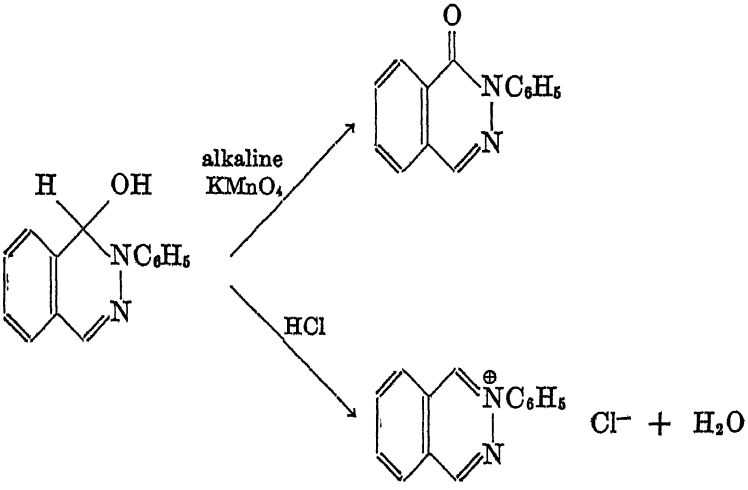
(25)

However, where there is a readily oxidizable group attached to a carbon of the azine ring, milder conditions yield a ketone (94).



(26)

Attention has previously been directed to the preparation of a 1-hydroxy-1,2-dihydrophthalazine derivative (equation 7d), and the behavior of this substance is of some interest. The methyl and ethyl ethers of this compound are readily accessible by warming it with the corresponding alcohols, and oxidation with alkaline potassium permanganate yields *N*-phenylphthalazone, while reaction with dry hydrogen chloride in benzene yields *N*-phenylphthalazinium chloride, rather than 1-chloro-2-phenyl-1,2-dihydrophthalazine (173) (equation 27).

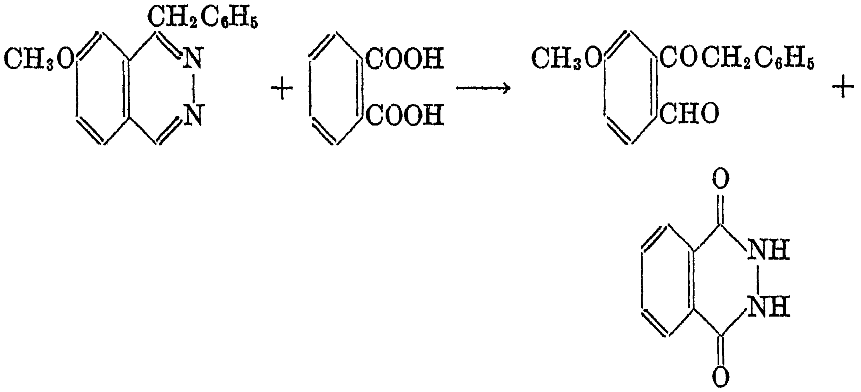


(27)

C. Ring cleavage

The azine ring is particularly stable, once it has been formed, but it has been found possible in a few instances to open it (2). Treatment of 1-benzyl-7-

methoxyphthalazine or 1-benzyl-6,7-methylenedioxyphthalazine with *o*-phthalic acid in ethanol at 100°C. for 6–8 hr. yielded the corresponding *o*-phenylacetylbenzaldehydes, which were isolated as their bisphenylhydrazones, the yields being reported as only moderate:

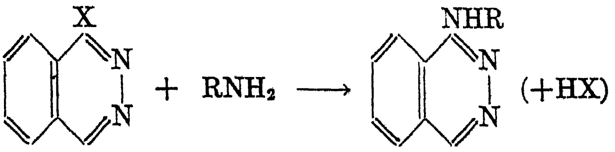


(isolated as
bisphenylhydrazone)

(28)

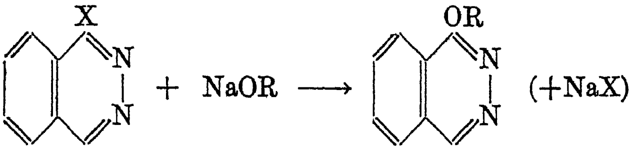
D. Activity of halogen derivatives

The activity of halogen attached to either or both carbons of the azine ring was recognized very early and is analogous to similar activity in 2- or 4-halogenoquinolines. In general the reactions of 1-halogeno- or 1,4-dihalogenophthalazines are with ammonia derivatives (primary and secondary amines) (40, 68, 78, 94),



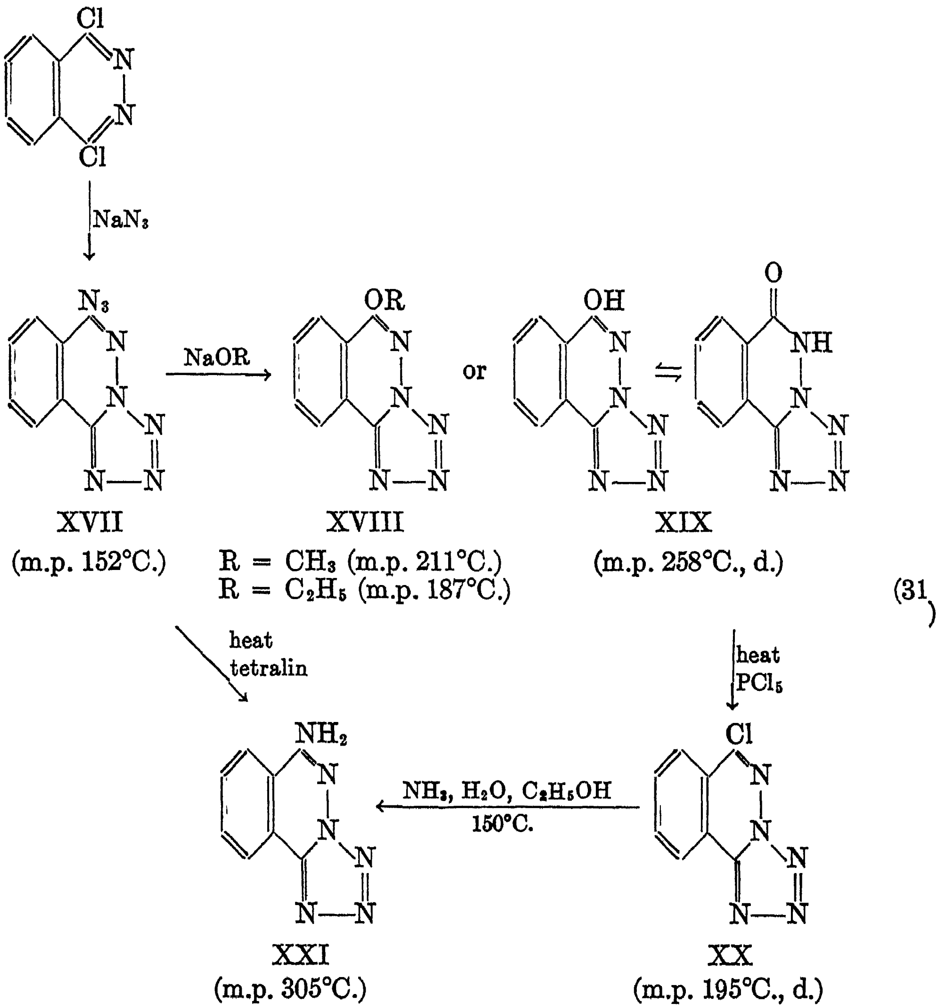
(29)

or with sodium salts such as the alkoxides to yield alkoxyphthalazines (20, 61, 62, 180, 184, 194).



(30)

In similar fashion an unusual series of compounds was prepared by Stollé and Storch (165) from 1,4-dichloro- (and 1,4-dibromo-) phthalazine and excess sodium azide in absolute alcohol at the reflux temperature (3 hr.):



XVII (m.p. 152°C.)

XVIII

R = CH_3 (m.p. 211°C.)

R = C_2H_5 (m.p. 187°C.)

XIX (m.p. 258°C., d.)

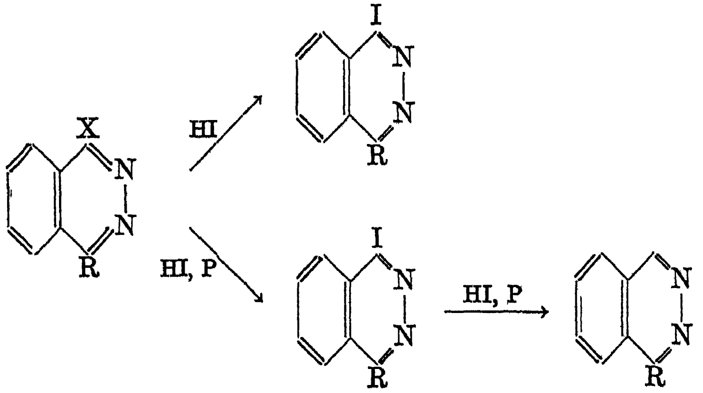
XXI (m.p. 305°C.)

XX (m.p. 195°C., d.)

(31)

The transformation of XVII into XVIII was accomplished by refluxing with methanolic sodium methoxide or ethanolic sodium ethoxide for 2 hr. XIX was obtained with the latter reagent upon prolonged refluxing (8 hr.). The tetralin reduction was accomplished in 85 per cent yield, and small yields of XXI were also obtained with amyl ether or xylene in place of tetralin. XIX forms an acetyl derivative (m.p. 165°C.), and XXI forms both a monoacetyl (m.p. 260°C. d.) and a diacetyl (m.p. 165°C. d.) derivative, the former in very poor yield only, and the latter in somewhat better yield. The authors assign to the latter the diacetylamino structure.

The course of reaction of C^1-halogenated phthalazines with hydriodic acid varies depending upon conditions. Simple replacement of chlorine by iodine occurs when hydriodic acid alone is used, or even in the presence of phosphorus; however, more vigorous treatment with hydriodic acid and phosphorus constitutes the earliest general method for the preparation of simple phthalazines (59, 94, 110, 194), as was noted in the section on the preparation of phthalazines.

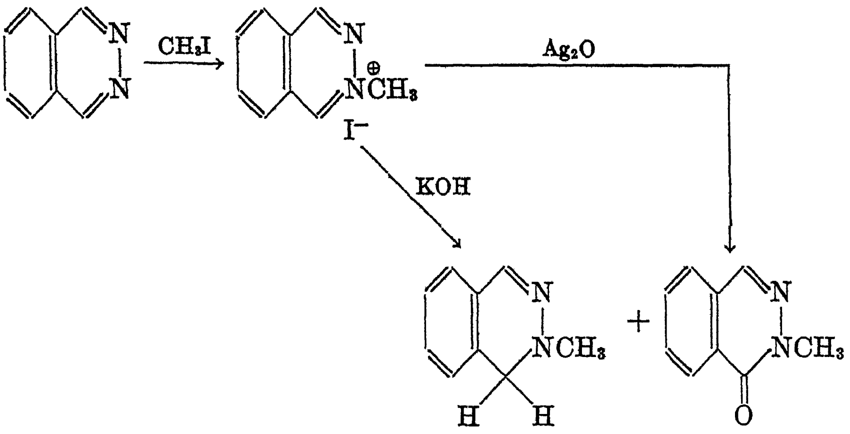


(32)

R = H, alkyl, aryl.

E. Alkylation

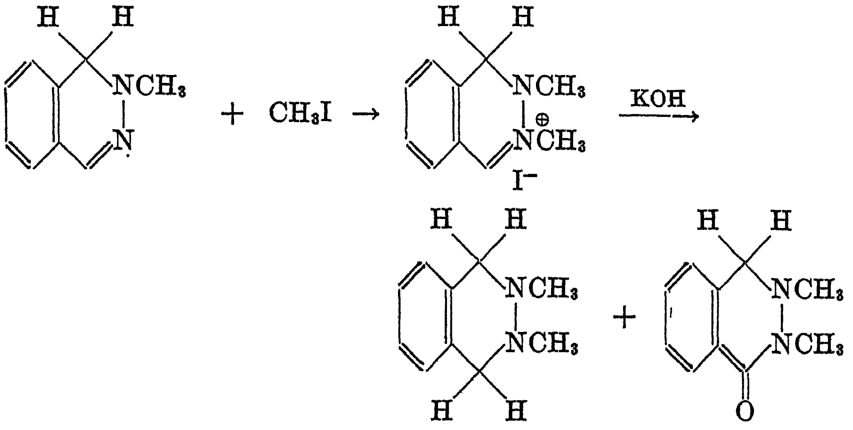
As with any amino compound the alkylation reaction is of great interest. Treatment of phthalazine or its *C*-alkyl derivatives with alkyl halides (especially methyl iodide and ethyl iodide) yields *N*-alkylphthalazinium halides (59, 60), which upon treatment with strong potassium hydroxide undergo disproportionation.



XXII XXIII

(33)

The structure of XXIII was established by synthesis and by its failure to dissolve in alkali; from the resultant structure, the structure of XXII (a steam-volatile oil) follows. XXII also reacts with methyl iodide, followed by potassium hydroxide, to yield a steam-volatile base, the reaction probably being:

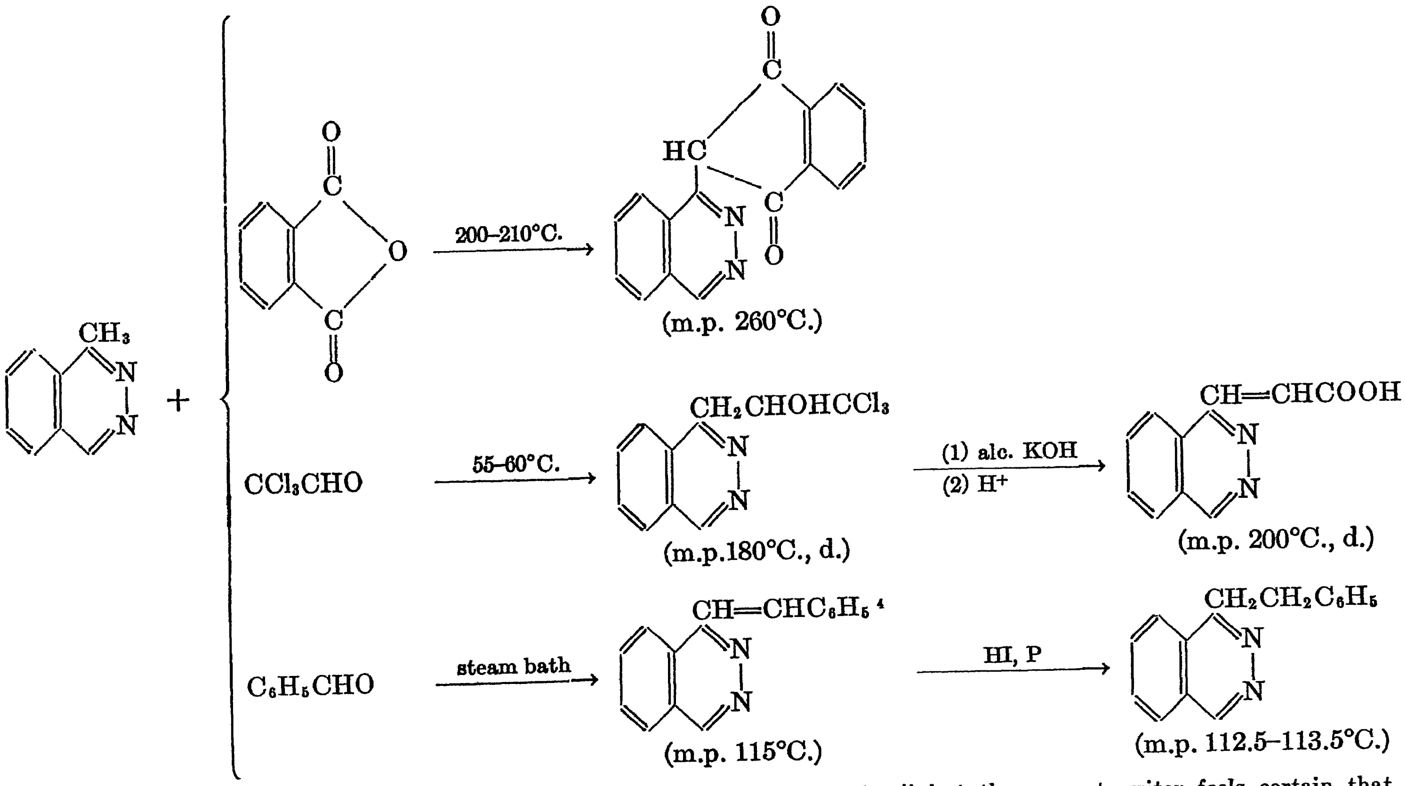


XXV XXVI (34)

but the structures of XXV and XXVI have not been investigated. The reactions illustrated by equation 33 are well established as oxidations and reductions, a silver mirror being deposited in the experiments involving silver oxide (equation 33); and the effect of potassium hydroxide is to form a phthalazinium hydroxide which apparently very readily disproportionates with the elimination of water to yield a 1,2-dihydro-2-methylphthalazine and 2-methylphthalazone. The disproportionation would appear to be more readily accomplished here than in the quinoline or isoquinoline series, since the corresponding quinolones and isoquinolones are usually prepared by oxidation of the quaternary bases with ferric chloride (159). Roser (126), however, reports an exactly analogous disproportionation with the *N*-methyl chlorides of quininic acid and cinchoninic acid, where the dihydroquinoline structure would seem to be stabilized by the 4-carboxyl group. Otherwise the dihydroquinolines must be regarded as less stable than the corresponding dihydrophthalazines; hence the equilibrium in any reduction will be very much in favor of the more fully aromatic structure of the quaternary bases. The fact that ferric chloride is used to prepare the usual quinolone types, while silver oxide is sufficient for the oxidation of the alkylphthalazinium salts to phthalazones, would seem to support the hypothesis that the dihydro structure is more stable in the phthalazine (and 4-carboxyquinoline) series than it is in the quinoline or isoquinoline series.

F. Activity of the methyl group

The behavior of 4-methylphthalazine is of considerable interest. The activity exhibited by a methylene group in the α- or γ-position of pyridine or quinoline (or the 1-position of isoquinoline) (159) is well known, and since in 1-methylphthalazine one encounters a structure analogous to that in 2-methylquinoline, or 1-methylisoquinoline, it is not surprising that 1-methylphthalazine should show enhanced activity in the methyl group. Such activity has been observed and reported by Gabriel and Eschenbach (59) as a part of the original extensive exploration of the field of phthalazine chemistry by Gabriel and his collaborators. A summary of the reactions studied is presented herewith.



(35)

---

[4] The original investigators refer to this substance as "cinnamenylphthalazine," but the present writer feels certain that "styrylphthalazine" will prove less confusing and hence more acceptable to the reader.

The reader's attention is called to the difference in the reaction between 1-methylphthalazine and phthalic anhydride and the reaction between 1-benzylphthalazine and phthalic acid (equation 28), where an exchange of the hydrazine ring system occurs in place of the condensation with the active methylene group. It is interesting to speculate regarding the influences responsible for such a difference and as to the possibility of effecting either type of reaction by simply varying reaction conditions.

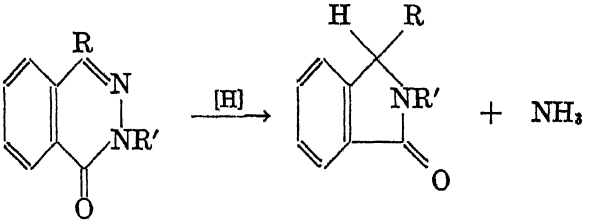
G. Salts and acyl derivatives

Finally, the simple phthalazines and the halogenated phthalazines, as might be expected from their amino structure, readily form a large variety of salts with various acids (e.g., hydriodic, hydrobromic, hydrochloric, picric, chloroplatinic, chloroauric, dichromic, and ferrocyanic) (20, 59, 60, 110). The tetrahydrophthalazines likewise form similar salts as well as *N,N'*-diacyl derivatives (62, 110).

VII. REACTIONS OF THE PHTHALAZONES

A. Reduction

The reduction of phthalazones has been studied by several investigators. Characteristically the reduction of phthalazones with strong reducing agents (e.g., tin or zinc and hydrochloric acid) yields 1-isoindolones (phthalimidines) (20, 34, 35, 55, 61, 117):

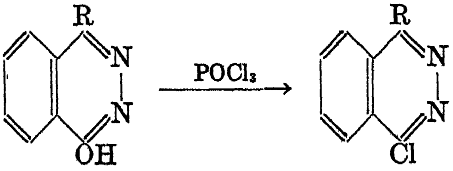


(36)

R = H, alkyl; R' = H, C_6H_5 (117).

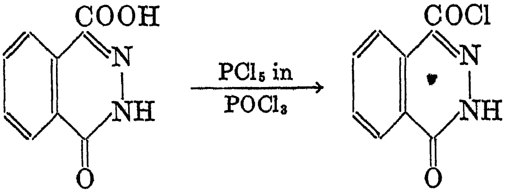
B. Reaction with phosphorus halides

In the preceding section the reactions of the C^1- or C^4-halogenophthalazines were described, and their use as the starting point for the synthesis of phthalazines was considered. These substances are regularly prepared by the interaction of the lactim form of phthalazone and phosphorus oxychloride (20, 35, 55, 57, 59, 61, 68, 94, 110, 163, 180, 184, 194).



(37)

It should be pointed out at this juncture that, despite the ability of the lactim to react with phosphorus oxychloride, this does not interfere with the preparation of the acid chlorides of phthalazone-4-carboxylic acids (55). The reaction in this instance is modified by using phosphorus pentachloride in phosphorus oxychloride solution:

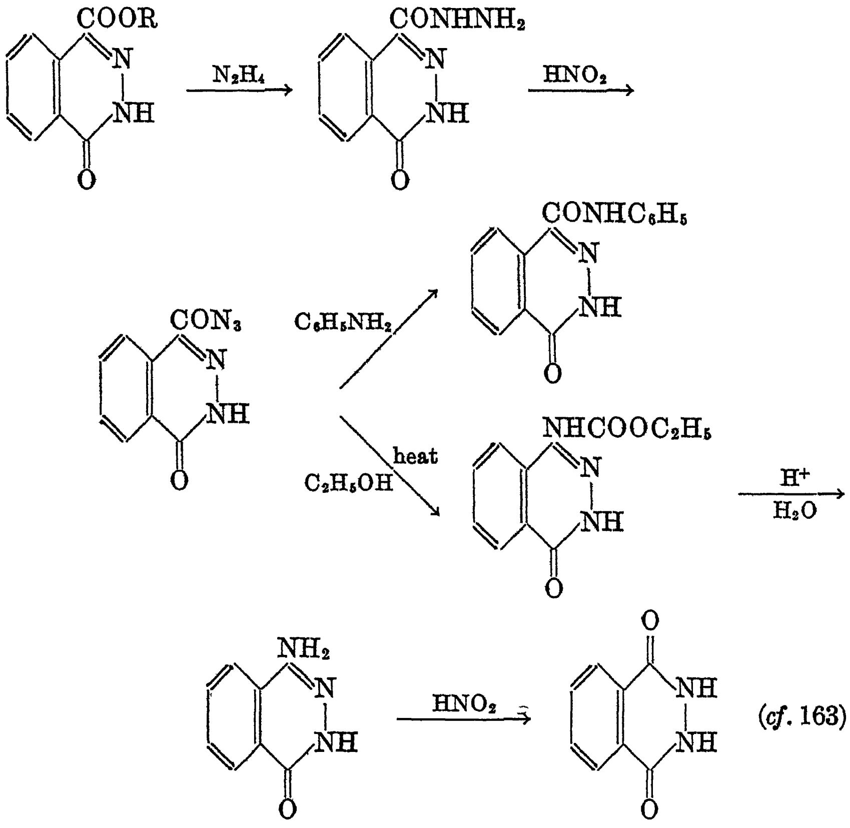


(38)

C. Phthalazonecarboxylic acids and their esters

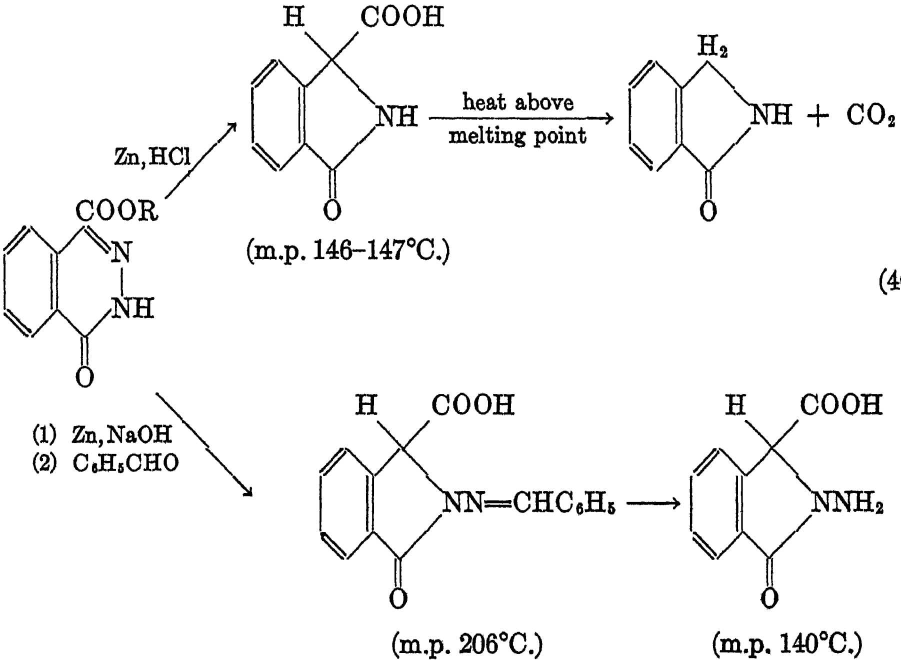
Other reactions of such carboxylic acids are also of interest. Decarboxylation is readily achieved by application of heat, usually above the melting point (55, 77, 180). The acids readily form metallic salts. Esters may be prepared from the acid chlorides (or by preparing the desired phthalazone-4-carboxylate from the corresponding phthalonic ester).

Reaction of an ester with hydrazine yields a hydrazide which exhibits the usual properties of hydrazides, including transformation to an azide which undergoes the Curtius rearrangement (160) and other reactions characteristic of azides such as replacement of the acid azide by RNH_2 (34).



(*cf.* 163) (39)

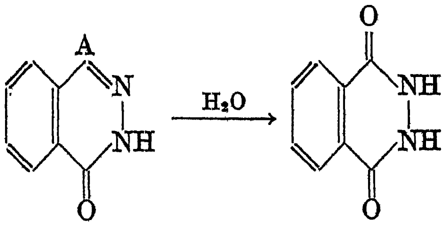
If the ester is subjected to reduction, the nature of the product varies with the conditions, the *N*-aminophthalimidine structure being isolated as the benzal derivative by treatment with benzaldehyde (34):



(40)

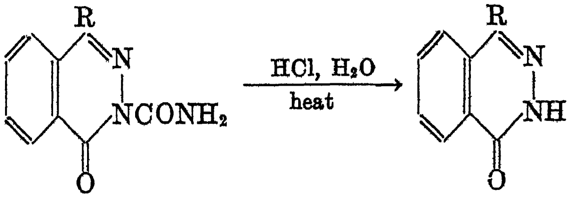
D. *Hydrolysis*

The hydrolysis of various derivatives of the phthalazones yields the expected products, but the phthalazone ring itself appears to resist hydrolytic cleavage.



(41)

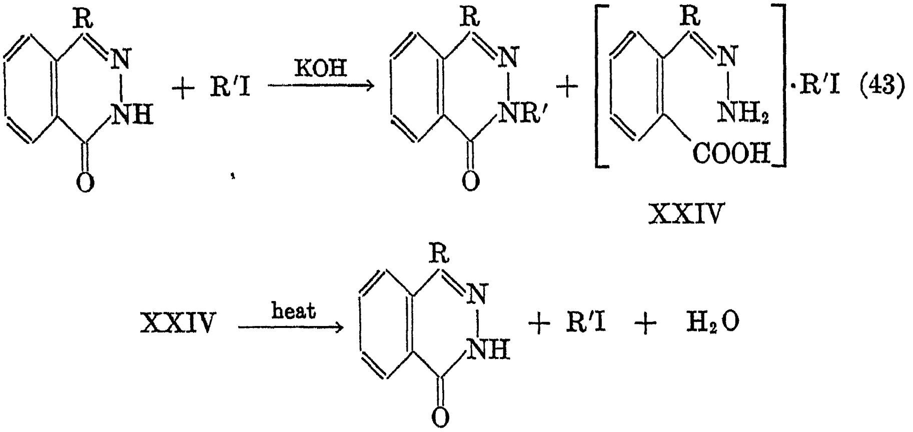
A = halogen (163); A = NHR (87).



(27, 90, 106). (42)

E. Alkylation

The alkylation of phthalazones (35, 59, 110, 184) proceeds as would be expected, with the formation chiefly of 2-alkyl derivatives, but the phthalazone ring may break simultaneously to give a substance (XXIV) of doubtful structure (59, 110):



(43)

It might be argued that XXIV arises as a consequence of *N*-alkylation in the 3-position, simultaneously with 2-alkylation. This would of course yield a quaternary iodide which would persist even after the opening of the ring, but the relatively low melting points (R = H, m.p. 170°C., d. (110); R = CH_3, m.p. 201°C., d. (59)) would seem to preclude the quaternary salt structure. The existence of an *N*-methyl hydroiodide as the structure for XXIV is extremely dubious under the conditions of the experiments (i.e., in the presence of excess alkali). Finally it should be noted that in the one experiment where sodium ethoxide was used in place of potassium hydroxide, no substance resembling XXIV was reported. This might be interpreted to mean that in the potassium hydroxide reactions XXIV was formed *after* a small quantity of the phthalazone had hydrolyzed, a reaction rather less probable when sodium ethoxide in ethanol was used, and that accordingly XXIV is an addition compound between methyl iodide and the hydrazone of phthalaldehydic acid. In any case XXIV is not a methylhydrazone hydroiodide: first because of the alkaline medium, and secondly because such a hydrazone would cyclize to yield 2-substituted phthalazones (*cf.* equation 6). Consequently it would appear that more investigation of this particular reaction is in order.

F. Acylation

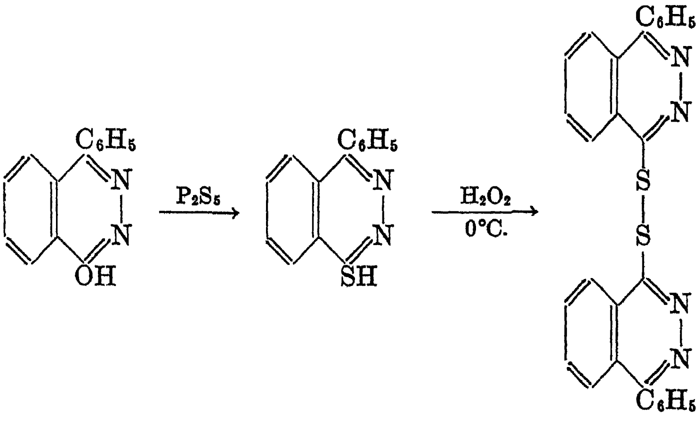
The behavior of phthalazones with acylating agents has not been extensively investigated. A few acetyl or benzoyl derivatives have been prepared (22, 142, 163, 184), and it is possible that these are *N*-acyl derivatives in spite of the assertion of Rowe and Peters that phthalazones must yield exclusively *O*-acyl derivatives. Their belief appears to be based upon the fact that the acetyl derivatives which they prepared were readily hydrolyzed to the free phthalazones by simply refluxing with alcohol (142). Of course it is well known that amides also may be deacylated by reaction with an alcohol, and since it has been demonstrated that wherever a reaction has been devised to yield an *O*-acyl derivative of an amide, the isomeric *N*-acyl amide has been obtained instead (23, 105), it would seem more probable that the acyl derivatives of the phthalazones are the *N*-acylated compounds, even though the non-aromatic system is thus apparently favored over the aromatic system of phthalazine.

G. Amphoteric character

The solubility of phthalazones in concentrated mineral acids attests to the basic character of N^3, while the solubility of the same substances in strongly alkaline solutions shows that the lactim form, in which the hetero-ring is fully aromatic, has a certain amount of stability, though apparently not enough to permit the isolation of salts (61, 142).

H. Reaction with phosphorus pentasulfide

Finally, the reaction of the lactim form of phthalazones with phosphorus pentasulfide has been found to yield sulfhydrylphthalazines (mercaptophthalazines), which would seem to have a possible use as accelerators in the vulcanization process (4) and which on oxidation yield disulfides:



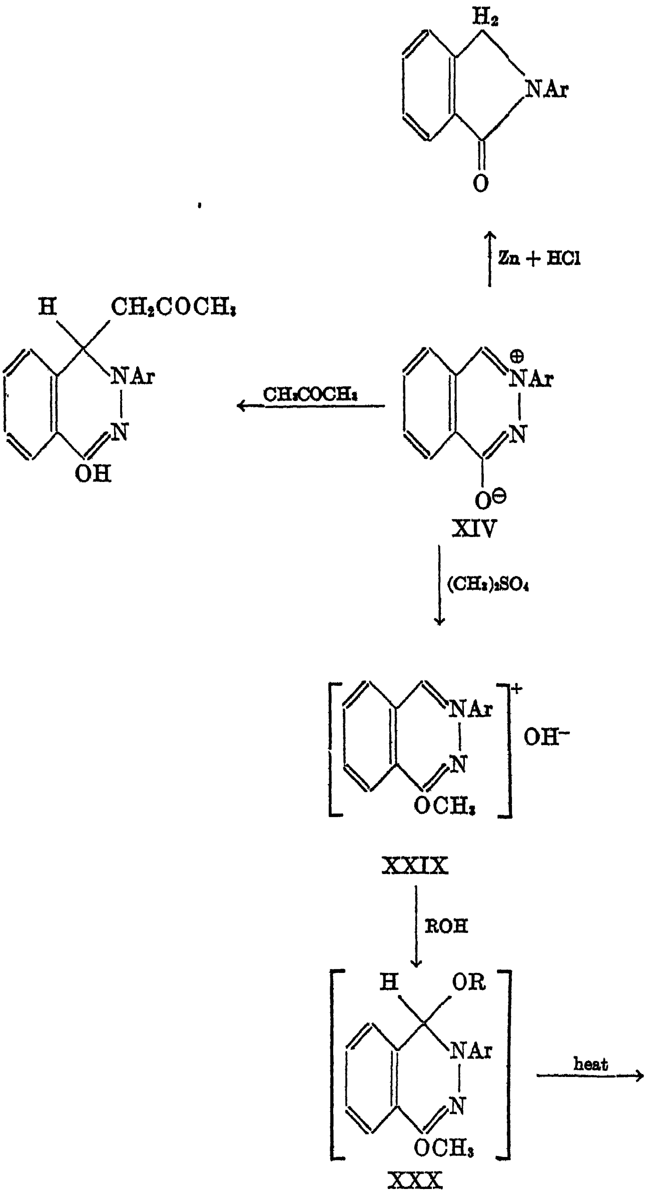
(44)

VIII. PSEUDOPHTHALAZONES

The preparation by Rowe and his associates of 3,4-dihydrophthalazone derivatives (XI; equations 10, 16, 17) has already been discussed (page 459); and the possibility of 1,4-oxidation of these 3,4-dihydrophthalazones to substances isomeric with and transformable into 2-arylphthalazones has also been described (equation 18). The 3-arylpseudophthalazones XIII and XIV are readily reduced to *N*-arylphthalimidines (127–145) just as are their isomers, the 2-arylphthalazones (20, 34, 35, 55, 61, 117) (*cf.* page 475).

Both XIII and XIV may be transformed into derivatives of phthalhydrazide by essentially similar reactions. Equations illustrating these and other transformations are given in table 2. These reactions are drawn from an important series of papers on the general subject of phthalazine chemistry by Rowe and his

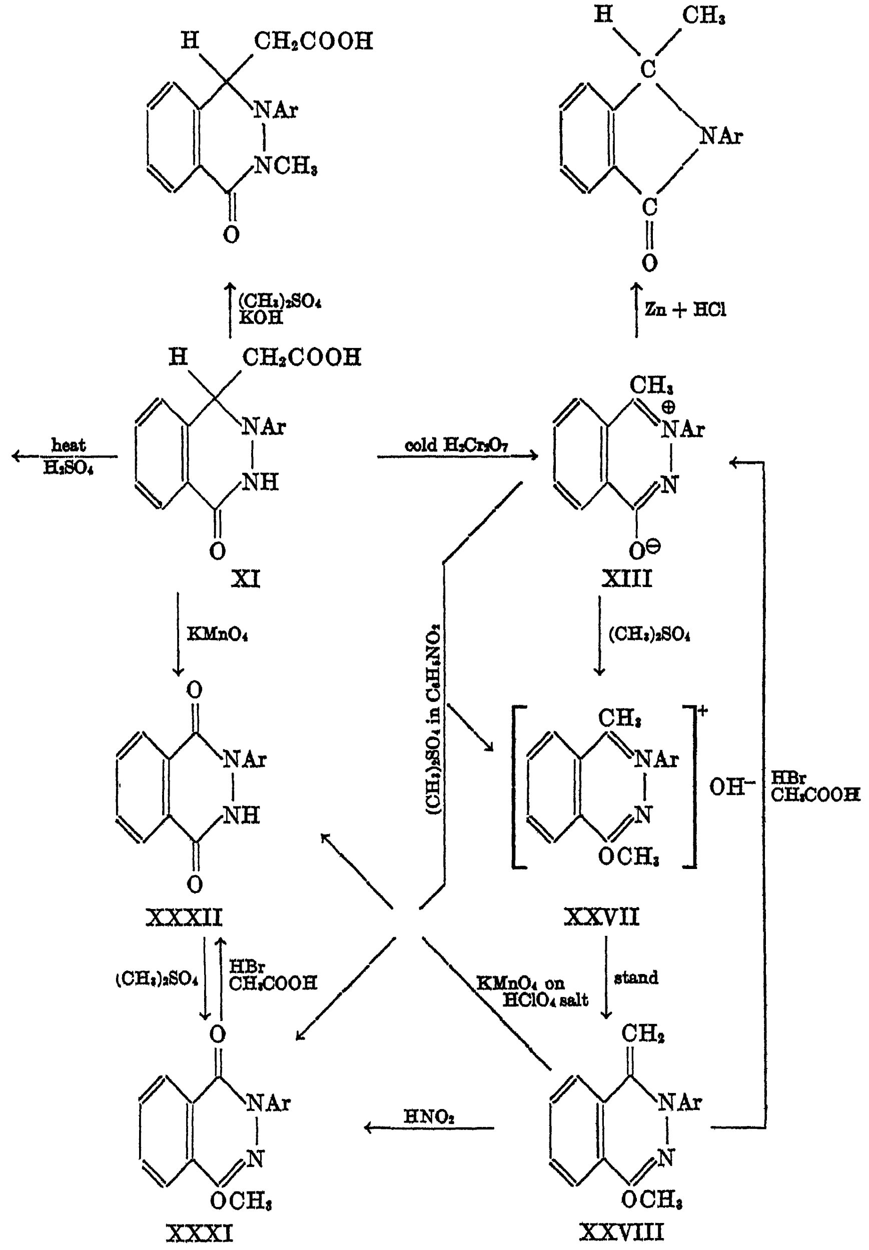
Pseudophthalazones



associates (127–145). The concept of structure was not altogether clear in the earlier papers, but starting with reference 141 the structures used in the present work were proposed with experimental data to support them. The nomenclature,

TABLE 2

available from 3-aryl-3,4-dihydrophthalazones

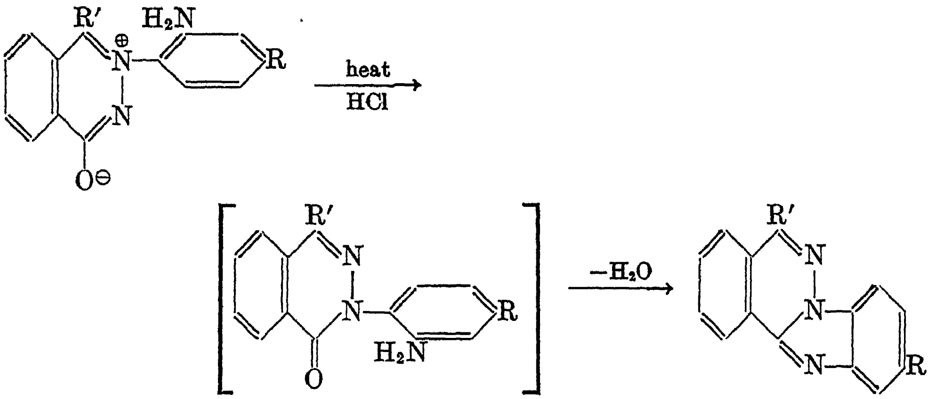


however, of the older papers was retained in order to preserve homogeneity in the series; but as stated in the introduction to the present paper, an attempt has been made to conform as closely to the current *Chemical Abstracts* nomenclature as possible. In order to avoid confusion in visualizing structural formulae from a systematic name, the term "pseudophthalazone" has been introduced for structures such as XIII and XIV, in which a betaine structure arises from the 3-aryl group. The present writer feels this to be more satisfactory than following the procedure of Rowe, who refers to the betaines as phthalaz-1-ones and the normal structures as phthalaz-4-ones. Thus three new syntheses are available for the preparation of *N*-arylphthalhydrazides (XXXII): direct oxidation of XI to XIII with subsequent transformation, or oxidation of XI to XIV with subsequent transformations. It should be mentioned that the reaction XI → XIII may also be effected by means of alcoholic potassium hydroxide, while the reaction XXVIII → XXXI may be effected by warming XXVIII with *p*-nitrosodimethylaniline. The addition of acetone to XIV was studied in only one instance (143).

The presence of the external methylene group in XXVIII on C^4 is clearly demonstrated by numerous reactions characteristic of such a structure (145). The reaction with nitrous acid (XXVIII → XXXI) is analogous to a reaction reported by Kuhn (89). In addition, the reactions in table 3 are selected from among the more interesting types.

If an *o*-nitro group is present in the 3-aryl group of the pseudophthalazone XI, certain modifications are introduced into the over-all reaction scheme (R = CH_3 or Cl), as illustrated in the reactions in table 4. The reactions XLI → XLII and XLI → XLIII occur simultaneously, with the latter reaction predominating. The tetrahydrophthalazine (XLII) obviously corresponds to a reduced form of XXXVIII.

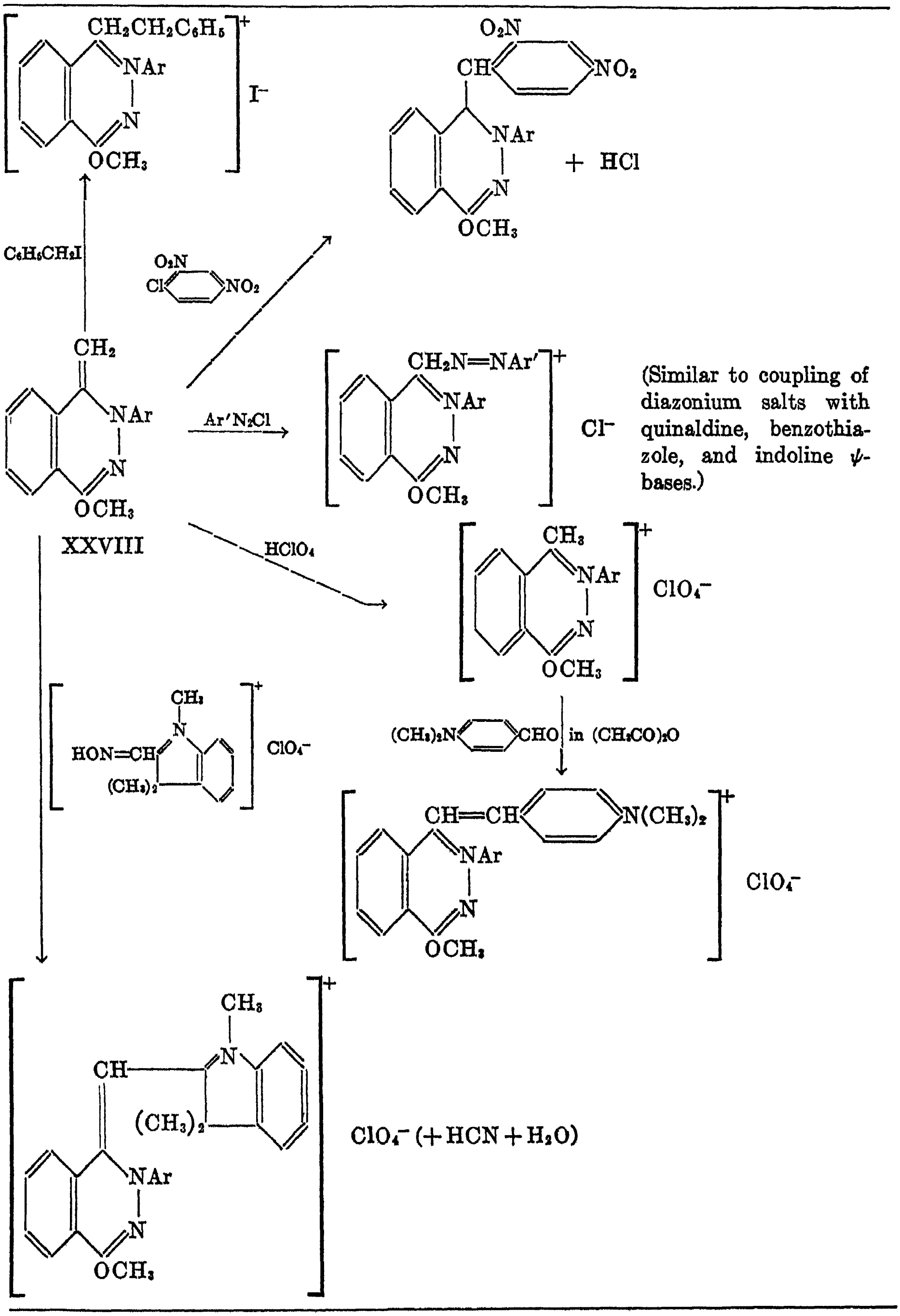
Objections may be raised, and with good reason, to structures XLI and XXXVII, even as intermediates as proposed by Rowe (127), since they obviously embody flagrant contradictions of Bredt's rule prohibiting double bonds at bridgeheads in bicyclo systems. Hence the following hypothesis is offered for consideration:



Where R′ = CH_3 (XXXVIII) the reaction has reached an end, but where R′ = H (XXXVIIIa) further reaction is possible, since hydrolysis of the original hetero-ring yields a labile system, the resultant aldehyde and hydrazine derivative

TABLE 3

Reactions of 1-methoxy-3-aryl-3,4-dihydro-4-methylenephthalazine

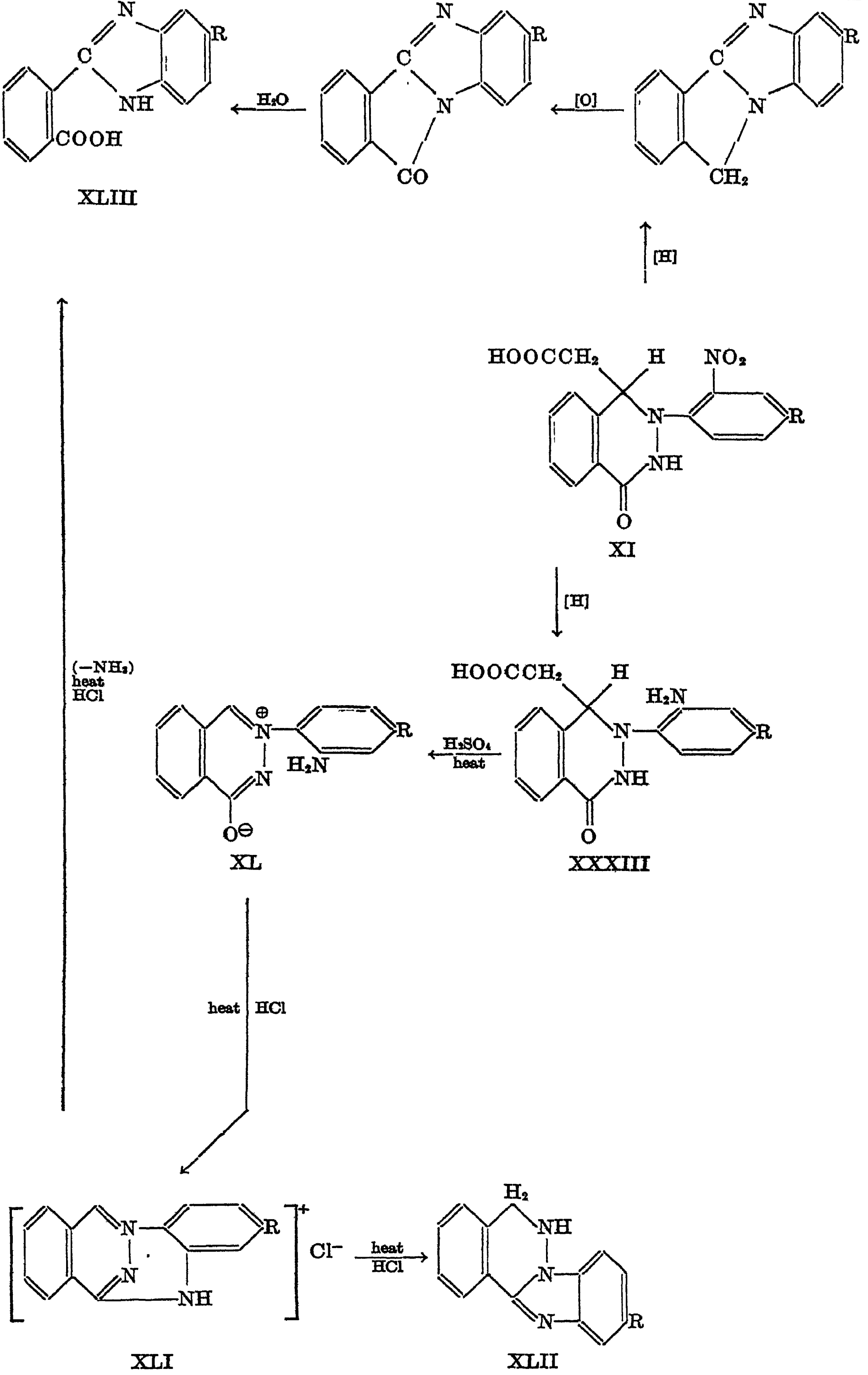


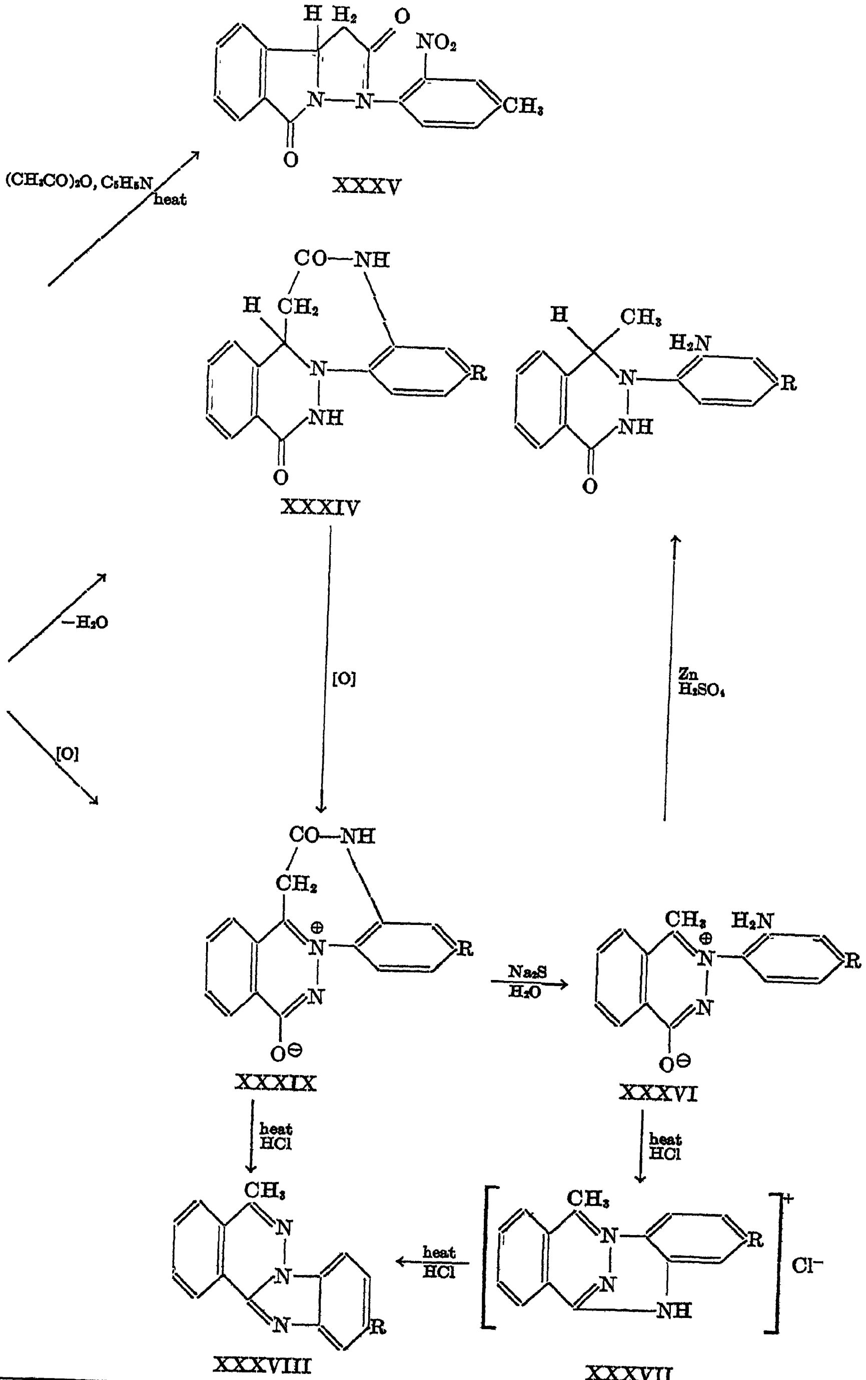
XXVIII

(Similar to coupling of diazonium salts with quinaldine, benzothiazole, and indoline ψ-bases.)

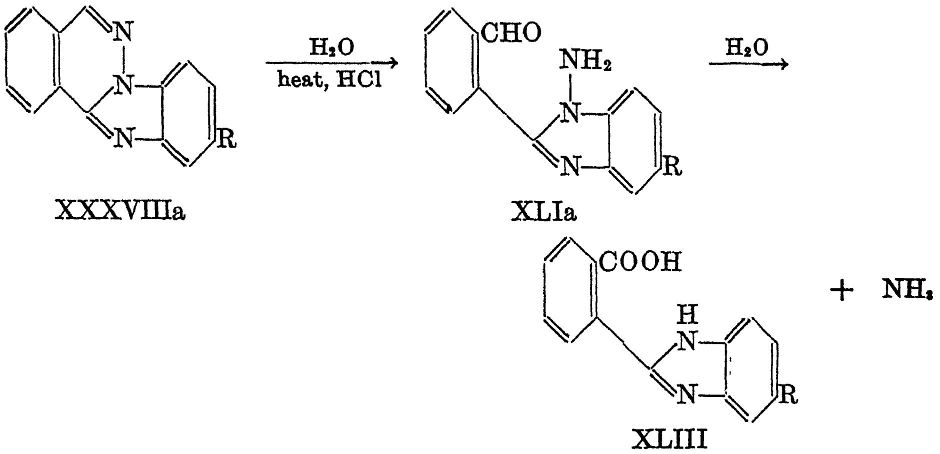
TABLE

Substances available from 3-[2′-nitroaryl]-



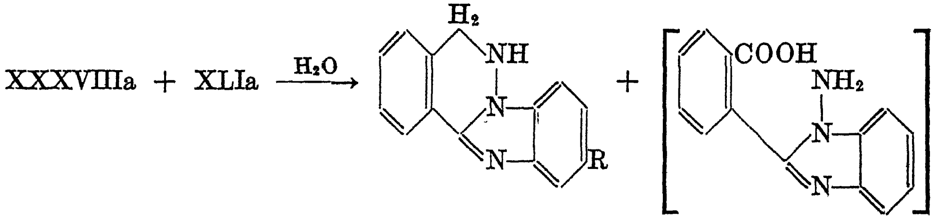

(CH₃CO)₂O, C₅H₅N
heat
XXXV
XXXIV
−H₂O
[O]
[O]
Zn
H₂SO₄
XXXIX
Na₂S
H₂O
XXXVI
heat
HCl
heat
HCl
heat
HCl
XXXVIII
XXXVII
Cl⁻

being capable of entering into an oxidation–reduction reaction which would not be possible with the ketonic hydrolysis product of XXXVIII:



XXXVIIIa XLIa XLIII

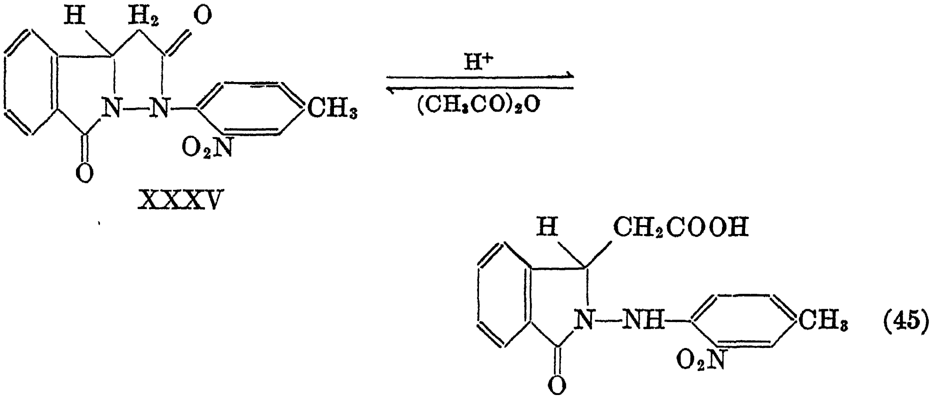
and



XLII XLIIa

The substance XLIIa (or its lactam) was not isolated, but it seems a reasonable possibility in view of the nature of the other reaction products. In any event it would be present in small amount since but relatively small quantities of XLII were isolated, the predominating reaction being the intramolecular oxidation–reduction yielding XLIII and ammonia.

The transformation XI → XXXV is unusual, and the lactam structure thus established opens reversibly:



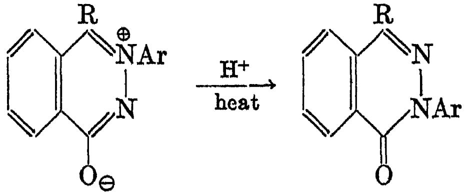
The lactam XXXIV (R = CH_3), however, is extraordinarily stable.

The rearrangements which occur in XL → XLII, XXXVI → XXXVIII, and XXXIX → XXXVIII are similar to those described for the less complex rearrangement of XIII into XV or XIV into XVI (page 463). Together they represent the general reaction involving the rearrangement of the betaine structure of the pseudophthalazones into the true phthalazone structure. This reaction is acid catalyzed and may well be called the Rowe rearrangement:

TABLE 5

Effect of substituents in migrating aryl group

Ar	R = H	R = CH_3
	per cent	*per cent*
4-Nitrophenyl	66	82
4-Nitro-2-methylphenyl	20	27
4-Nitro-2-chlorophenyl	—	49
4-Nitro-2-bromophenyl	—	27
4-Nitro-2,6-dichlorophenyl	46	17
4-Nitro-2,6-dibromophenyl	20 (10 hr.)	—
3-Nitrophenyl	14	25
2-Nitrophenyl	—	65
2-Nitro-4-methylphenyl	36	53
2-Nitro-4-chlorophenyl	68	74



(46)

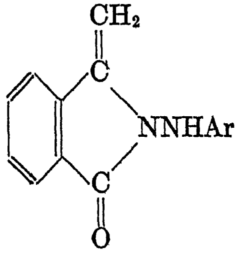
XIII: R = CH_3 XV: R = CH_3
XVI: R = H XVI: R = H

This reaction has been studied with particular attention to per cent conversion, rates, and the general nature of the rearrangement (127). It is best effected by heating the pseudophthalazone with 1.2 *N* hydrochloric acid in a sealed tube for 6 hr. The ease of conversion depends largely upon the nature of the aromatic group and to a certain extent upon the nature of R. In table 5 are listed the conversion yields expressed as per cent after heating at 180°C. for 6 hr.

The following general observations are possible: 2- and 4-nitro groups facilitate the rearrangement, while a 3-nitro group does not; halogens in the 2- and/or 4-positions and methyl in the 2- and the 4-positions appear to retard the reaction.

From rate studies the reaction appears to be unimolecular, the rate constant varying from 4×10^{-4} to 48×10^{-4}. The intramolecular character of the rearrangement was established by using mixtures of pseudophthalazones (different Ar and R groups) in the rearrangement reaction. In all experiments no exchange was observed.

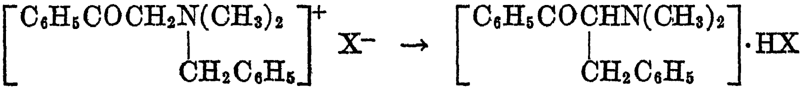
The course of the reaction was studied, and it was found that an intermediate of structure



XLIV

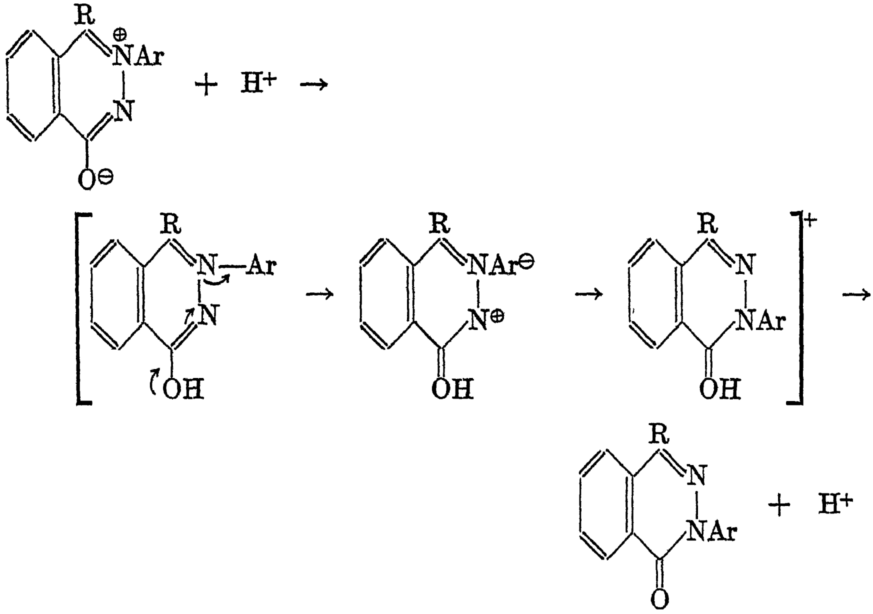
occasionally was formed at the reflux temperature from XIII. Such substances were stable against bromine addition and resisted reduction by iron in acetic acid; but they were capable of transformation into XV by prolonged heating (180°C. in sulfuric acid). However, since the rearrangement also occurred with XIV, where such an intermediate is obviously impossible, it was concluded that the formation of such intermediates did not indicate the actual course of the reaction XIII → XV, but represented rather a side reaction, which also yielded some demethylated product (XVI) as well as the chief product (XV).

The mechanism proposed by Rowe is likened by him to the mechanism suggested for the rearrangement of phenacylbenzyldimethylammonium salts (164):



$$\left[\begin{array}{l}C_6H_5COCH_2N(CH_3)_2 \\ \qquad\qquad\quad | \\ \qquad\qquad CH_2C_6H_5\end{array}\right]^+ X^- \rightarrow \left[\begin{array}{l}C_6H_5COCHN(CH_3)_2 \\ \qquad\qquad | \\ \qquad\quad CH_2C_6H_5\end{array}\right]\cdot HX \qquad (47)$$

The Rowe rearrangement is formulated as follows (127):

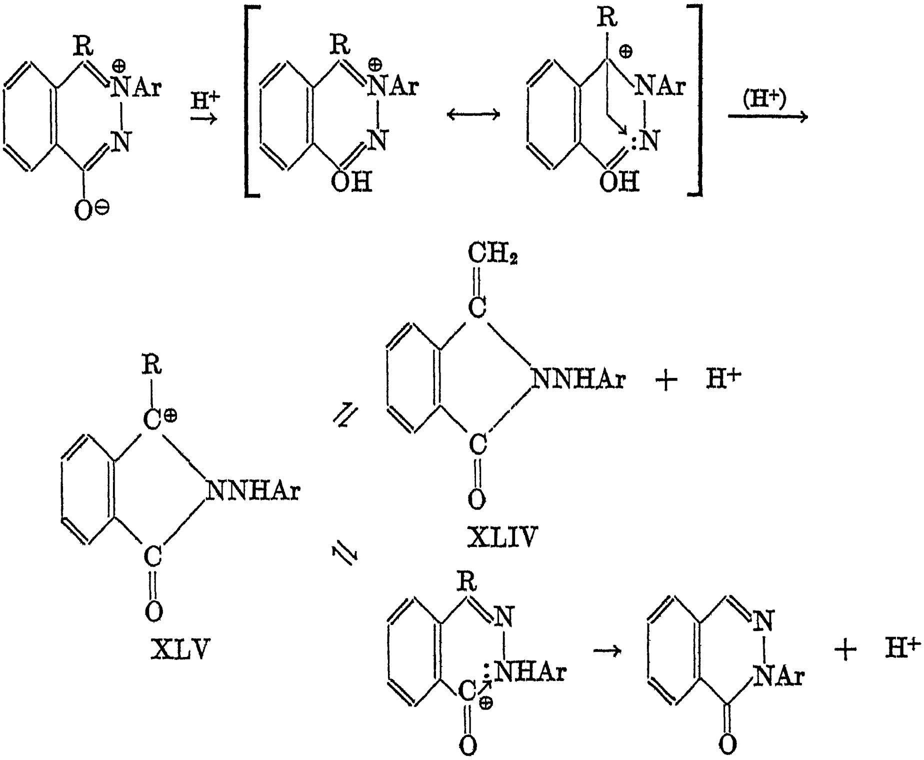


(48)

The intramolecular reaction thus described is completely analogous to other rearrangements involving carbonium ions, in which a group with its bonding pair of electrons shifts to an adjacent atom (*cf.* 72).

Rowe's isolation (127) of compounds such as XLIV suggests an alternative mechanism in which the rearrangement occurs through the intermediate formation of a five-membered ring, followed by a second rearrangement enlarging the ring to six members again (the latter step is analogous to the transformation of *N*-aminophthalimides into phthalhydrazides, which, however, is base catalyzed, as discussed on page 465). Such a course for the reaction was originally discounted by Rowe, since such an intermediate five-membered ring structure, as noted above, is impossible where the C^4 of the original pseudophthalazone carries a hydrogen atom instead of a methyl group; but this objection is valid only so long as one considers that the intermediate must be stable, capable of finite existence, or actually isolable.

The following alternative mechanism (*cf.* equation 51, page 492) is proposed for the Rowe rearrangement, and its validity might be tested by the use of isotopic nitrogen, since it requires that the aryl group remain attached to the same nitrogen throughout rather than being transferred as required by Rowe's mechanism. The driving force initiating the formation of the intermediate XLV may be considered an attack of a proton on the nitrogen carrying the aryl group, thus displacing the C^+ which subsequently ejects the original proton.



XLIV

XLV

This course of reaction obviously is independent of the nature of R, and Rowe's isolation of substances with the structure XLIV may be explained by the reaction XLV → XLIV + H^+ (where R = CH_3), where the intermediate XLV, under conditions mild enough to permit its formation without immediate rearrangement, stabilizes itself by ejecting a proton. Such stabilization is impossible where R = H; hence the only reaction possible is the complete rearrangement to the true phthalazone structure, which is possible only under conditions more drastic than those required for the transformation yielding XLIV. Finally, the transformation of XLIV into the true phthalazone structure, which as noted above occurs under conditions suitable for the complete rearrangement, may be regarded as an addition of a proton to XLIV, regenerating XLV (R = CH_3), which then follows through to the true phthalazone, losing a proton as the final transformation occurs.

IX. REACTIONS OF THE PHTHALHYDRAZIDES

A. *Oxidation and reduction*

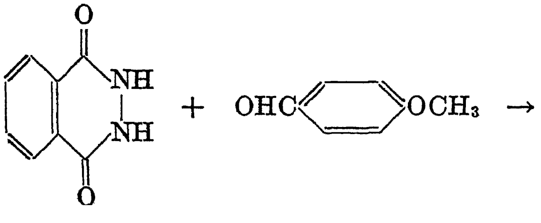
Both the oxidation and the reduction of phthalhydrazide have been studied by Curtius (31), who reported that the substance was oxidized by strong oxidizing agents to phthalic acid and nitrogen, but that it was completely indifferent to reducing agents except for an apparent cleavage into phthalic acid and hydrazine upon heating with zinc and concentrated hydrochloric acid. The inertness to reducing agents makes possible the reduction of nitro groups in the carbocyclic ring (synthesized from substituted phthalic acids) and subsequent reactions of the new amino group (32, 33).

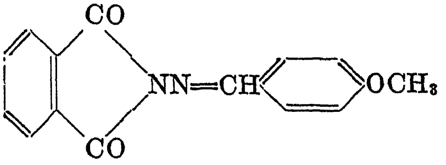
B. *Resistance to substitution and hydrolysis*

In the same paper phthalhydrazide was shown to resist sulfonation, nitration, and bromination under the usual conditions for these reactions, and indeed to resist even very vigorous attempts to hydrolyze the azide ring.

C. *Isomerization*

The conversion of *N*-aminophthalimides to the isomeric phthalhydrazides has been considered in the section on the preparation of phthalhydrazides; until comparatively recently it was thought that this process was not reversible. However, in a preliminary study of the preparation of phthalhydrazides Drew and Hatt were able to show that such a reversal was indeed possible and to suggest a mechanism for it (45). A chance observation some years earlier by Mihăilescu (100) was wrongly interpreted to indicate that he had obtained *N*-aminophthalimide from a reaction between phthalic acid and hydrazine. It was later shown (122) that Mihăilescu actually had prepared the isomeric phthalhydrazide. The reaction leading to this confusion was correctly interpreted by Drew and Hatt as follows:

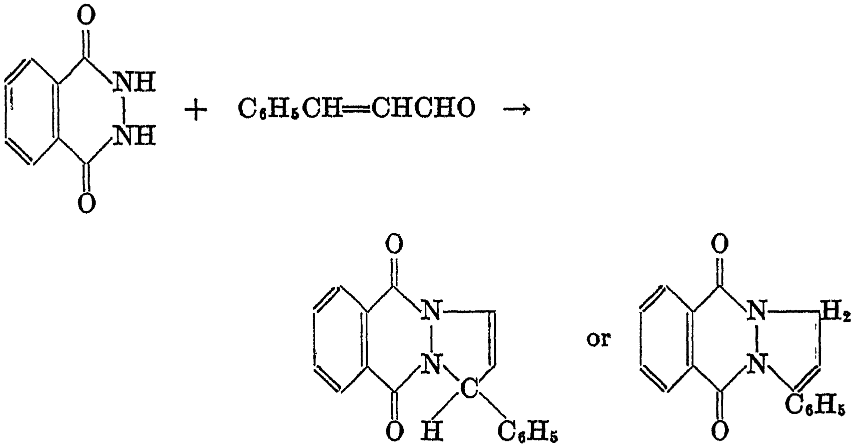




(49)

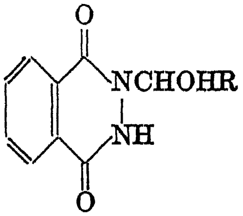
The reaction is unexpected, and it is not surprising that it was mistaken for a condensation of *N*-aminophthalimide with anisaldehyde to yield the same product.

Drew and Hatt further demonstrated that the reaction may be a general one for aromatic aldehydes, and in the reaction between phthalhydrazide and cinnamaldehyde is to be found a clue to the reaction mechanism.

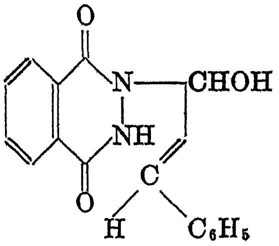


(50)

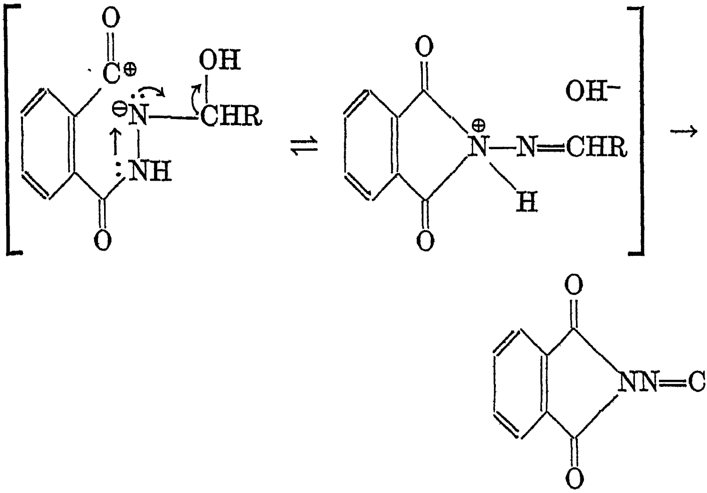
Upon first inspection this reaction would appear to be anomalous (*cf.* reaction 49), but it is interpreted to show that the primary reaction of aldehydes with phthalhydrazide is *addition* to yield:



or for cinnamaldehyde to yield:



which then cyclizes with loss of water to yield a tricyclic structure (equation 50) which prevents the more characteristic rearrangement from occurring. Where no such cyclization is possible the rearrangement is illustrated as follows:

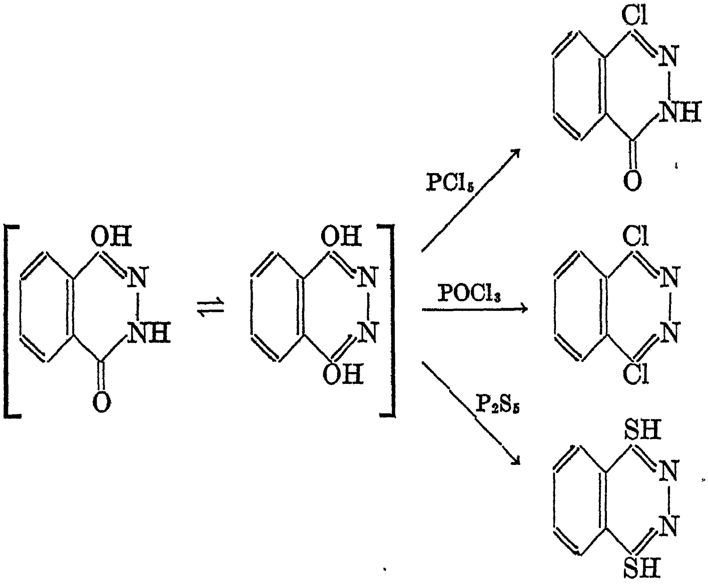


(51)

Drew likens the rearrangement to the pinacol rearrangement, but the present writer prefers to consider it on its own merit for the present.

D. Reactions with phosphorus halides and phosphorus pentasulfide

The existence of phthalhydrazide in either the lactam–lactim or the dilactim form is possible and thus permits the ready preparation of phthalazone and phthalazine derivatives (4, 122, 195):



(52)

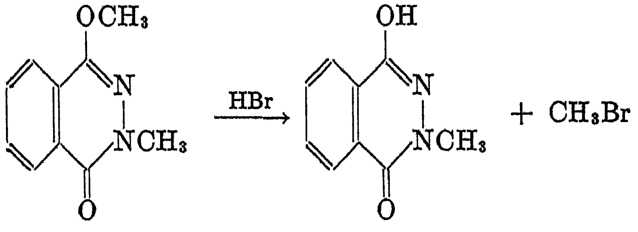
E. Acidic character

Solutions of phthalhydrazide in water are acid to litmus (122), and the preparation of metallic salts (monovalent) from various phthalhydrazides has long been a well-known reaction (21, 31, 76, 122). Indeed, phthalhydrazides are sufficiently acidic to yield stable salts with ammonia or with hydrazine (32, 33, 113). This immediately suggests the existence of phthalhydrazide as the lactam–lactim structure in aqueous media, but since there is undoubtedly a tautomeric equilibrium, any arguments as to the absolute structure in solution are without significance. At most one might state that the lactam–lactim form predominates sufficiently to cause an acid reaction to litmus.

F. Alkylation and acylation

By far the most controversial problem in phthalhydrazide chemistry is the nature of the various alkyl and acyl derivatives. Very early Curtius reported the preparation of what he believed to be *N*-methylphthalhydrazide, m.p. 235°C. (31), from a reaction between silver phthalhydrazide and methyl iodide at an elevated temperature and pressure. Subsequently Rădulescu (122) reported what he believed to be an *O*-methylphthalhydrazide (i.e., 4-methoxyphthalazone), m.p. 232°C., but this was subsequently identified with Curtius' product (45, 142). True 4-methoxyphthalazone, m.p. 187–188°C., may be obtained by refluxing silver phthalhydrazide with methyl iodide in methanol (142; *cf.* 76).

Rădulescu also reported the preparation of 1,4-dimethoxyphthalazine, m.p. 77°C., by the alkylation of phthalhydrazide, but Rowe and Peters (142) repeated this work and obtained a substance similar to that of Rădulescu but melting after extensive purification at 93°C. Further, Rowe and Peters were able to demethylate their product to the known *N*-methylphthalhydrazide (melting point variously reported in the range 232–238°C.):

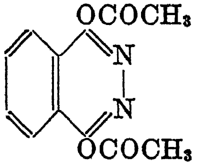


(m.p. 93°C.) (m.p. 238°C.) (53)

The melting point of 2-methyl-4-methoxyphthalazone is quite in line with that of 2,4-dimethylphthalazone (respectively 112°C. (142; *cf.* 59) and 109–110°C.), as are its mildly basic properties which originally suggested to Rădulescu the (erroneous) 1,4-dimethoxyphthalazone structure; the compound having this structure was obtained by Drew and Garwood (42) and found to melt at 121°C. However, 2,3-dimethylphthalhydrazide, m.p. 175–176°C., has been prepared by Drew and his collaborators from *N*,*N*′-dimethylhydrazine (45); various other

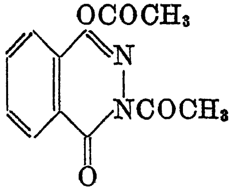
N,N'-disubstituted (alkyl and aryl) phthalhydrazides have been similarly prepared (85, 96).

The problem of acetylation is rather more difficult to settle by purely chemical methods. Ever since Curtius (31) first reported a diacetylphthalhydrazide, m.p. 114°C., the structure of acylphthalhydrazides has been in doubt. Curtius without hesitation assigned an N,N'-diacetyl structure to his product, and his precedent has been followed by most subsequent investigators (32, 64, 113). Rădulescu (122) reported the synthesis of two diacetylphthalhydrazides which he believed to be:



(m.p. 126°C.)

and



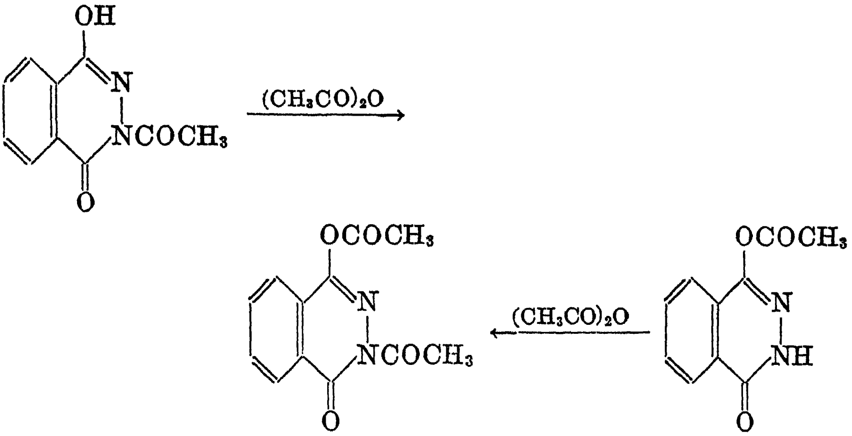
(m.p. 133°C.)

The lower-melting isomer he described as stable, while the higher-melting compound he found to be labile. Subsequently Rowe also investigated the acetylation of phthalhydrazide (142), but he was able to obtain only the lower-melting isomer to which he assigned the 1,4-diacetoxyphthalazine structure preferred by Rădulescu for his lower-melting derivative. The basis for Rowe's assignment was simply the very ready hydrolysis of his product.

This phase of the controversy finally yielded to direct experimental proof. Drew (45) produced incontrovertible evidence that the compound melting at 133–134°C. (which upon careful purification melted at 139–140°C.) was indeed the 2-acetyl-4-acetoxyphthalazone, as claimed by Rădulescu. Simultaneously the question of monoacetylphthalhydrazide was also partially settled: the existence of *two* monoacetyl derivatives with very nearly the same melting point, 172–173°C. and 175–176°C., was established, since the two substances markedly depressed each other's melting point. The latter substance is produced by direct acetylation or by treatment of phthalhydrazide with acetyl chloride in pyridine, while the former is produced by boiling the diacetyl derivative with alcohol (45). Drew and Hatt wisely refrained from a positive assignment of structure to their two monoacetylphthalhydrazides.

Heller and his collaborators (76) prefer the O-acetyl structure for the monoacetylation product from acetyl chloride, as do Rowe and Peters (142), but the latter also may have obtained the N-acetyl isomer as well, since their "1,4-diacetoxyphthalazine" (now recognized as 2-acetyl-4-acetoxyphthalazone) yielded what they thought was the product of monoacetylation upon hydrolysis. They overlooked the non-identity of their monoacetyl derivatives by failing to take a mixed melting point on them.

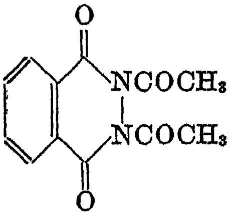
Drew's evidence for the correct structure of the diacetyl derivative is based upon the acetylation of each of his different monoacetyl derivatives to yield the *same* diacetyl derivative:



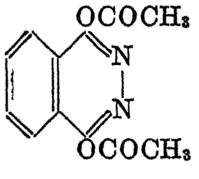
(54)

Obviously for this proof it is not necessary to know the absolute structure of either monoacetyl derivative, only that there are two *different* monoacetylphthalhydrazides. Attempts to prove the structure of either of the monoacetyl derivatives by synthesis of the *N*-acetyl isomer using either acetyl- or *sym*-diacetylhydrazine failed, since only *N*-acetamidophthalimide was isolated. Except for conclusive evidence that *alkylation* yields first an *N*-alkyl derivative and then an *O,N*-dialkyl derivative (197), except where a third six-membered ring can be formed (75), there is no argument sufficiently valid for an absolute structure assignment, and the exact nature of the two monoacetylphthalhydrazides will not be known with any certainty until they can be examined in the infrared, where one may expect to observe marked differences between *N*-acetyl and *O*-acetyl compounds. The only authenticated *N,N*-diacylphthalhydrazides are obtained where a third six-membered ring is formed (45).

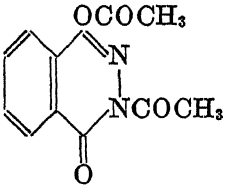
The status of acetylphthalhydrazides may be summarized as follows:



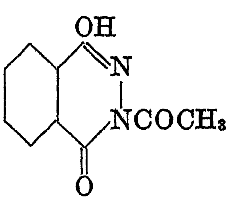
(m.p. 114°C.)
Curtius (31) (?)



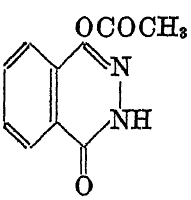
(m.p. 126°C.)
Rădulescu (122) (?)



(m.p. 139–140°C.)
Drew and Hatt (45)

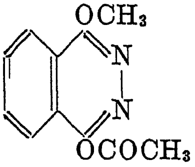


(?) {(m.p. 172–173°C.)
(m.p. 175–176°C.)
Drew and Hatt (45)



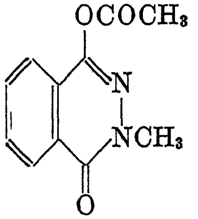
(?) {(m.p. 172–173°C.)
(m.p. 175–176°C.)
Drew and Hatt (45)

Rowe and Peters also investigated the formation of acetyl derivatives from both *O*- and *N*-methylphthalhydrazide (142) and reported the existence of an *O*-acetyl derivative in each instance:



(m.p. 137°C.)

and



(m.p. 142°C.)

Once again the basis for their assignation of structure is the ready hydrolysis of the acetyl group, but in view of incomplete data and the misinterpretation of the structure of the diacetylphthalhydrazides in the same paper, extreme caution must be used in accepting these as the correct structures until further experimental evidence is available.

G. N-Substitution yielding acid derivatives

Finally, several investigators have reported the preparation of phthalhydrazides with carboxylic acid or ester groups attached to the nitrogen by the reaction of a salt of phthalhydrazide with carbethoxy chloride or ethyl chloroacetate (31, 32, 76, 113) see page 497. The former, as might be expected, yields phthalhydrazide upon hydrolysis of the ester group, but the latter yields the phthalhydrazidoacetic acid. It is interesting to note that despite several attempts to hydrolyze the latter substance to hydrazinoacetic acid (*N*-aminoglycine), no such product was isolated (31).

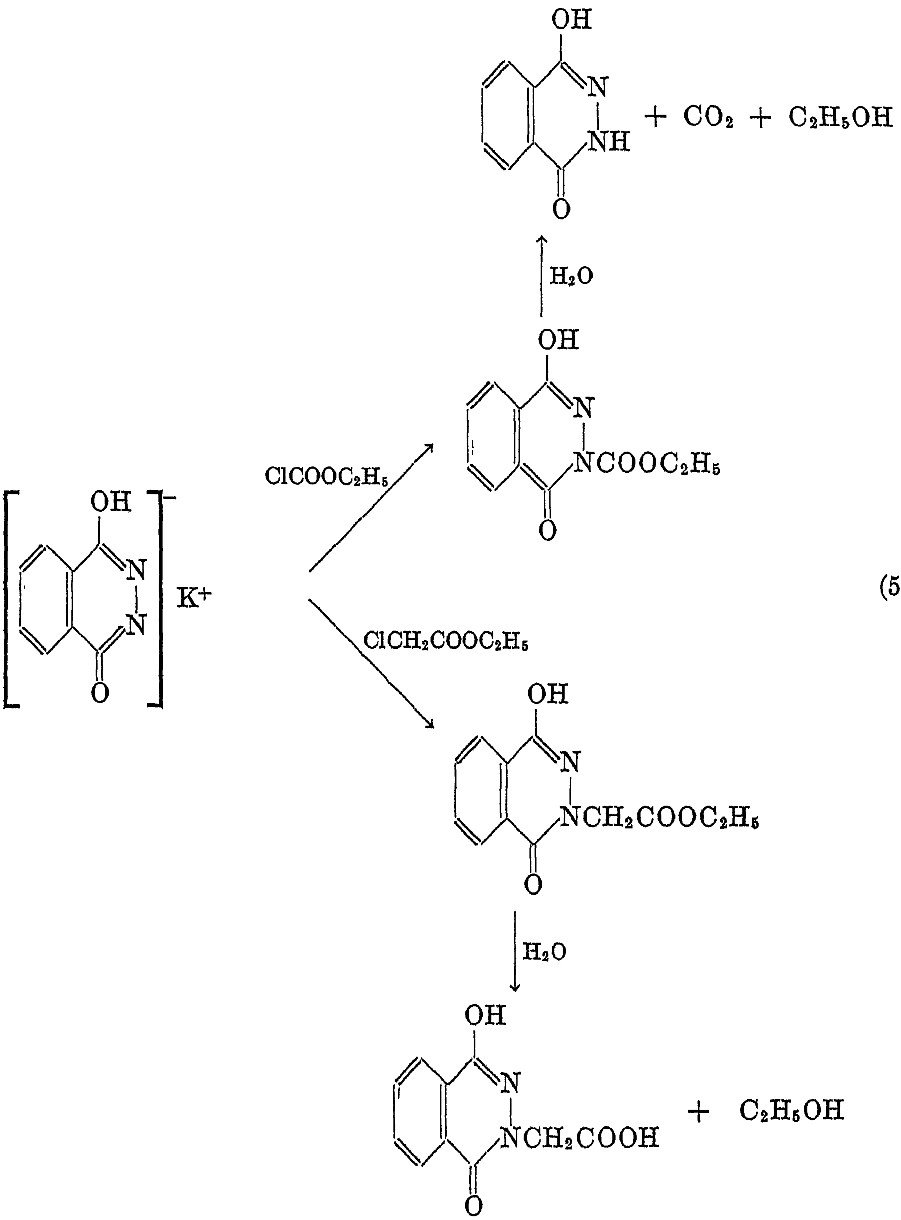
The preparation of an *O*-carbethoxy derivative (76) is to be discounted, owing to lack of sufficient evidence. The same author reports a 2,3-dicarbethoxy derivative formed in the same reaction; once again conclusive experimental data is lacking, and arguments based on the relative ease of hydrolysis of such compounds are specious.

X. CHEMILUMINESCENCE

Certain phthalhydrazides are capable of marked chemiluminescence in the course of being oxidized. In particular, 5-aminophthalhydrazide, which has become generally known as "luminol," exhibits this phenomenon in a rather spectacular fashion. These substances are structurally the same as the ordinary phthalhydrazides, and their synthesis is achieved by the same general procedures (*cf.* Section IV and references 42, 44, 46, 83, 178, 189, 193, 196).

A. Nature of the phenomenon

The underlying cause for chemiluminescence seems to be an oxidation reaction involving hydrogen peroxide (36, 73, 74, 82) or ozone (18). There have been observed instances of chemiluminescence in the presence of oxygen alone dissolved in water, but activation, achieved by means of ultrasonic vibration, would



(55)

seem either to produce hydrogen peroxide *in situ* (53) or to activate the dissolved oxygen directly in some other manner (17). Details for producing a spectacular display of chemiluminescence from hydrogen peroxide and luminol for lecture demonstration purposes are readily available (82).

B. Promoters or accelerators

While the phenomenon is observable without them, certain substances act as very strong promoters or accelerators: hemoglobin (18, 91, 123, 148, 149, 161, 169, 188); certain plant chemicals (124, 150); certain inner complex salts such as phthalocyanines (26, 150, 174) and salicylaldehyde–ethylenediamine–ferric chloride (174, 188); and various metallic ions —cupric, ferrous, manganous, cobaltous, and cobaltic, but not nickel (63, 161, 166, 176). There are also a few specific inhibitors: potassium cyanide, sodium sulfide, hydroquinone, acetone, pyridine, phenol, and others (186, 187).

C. Applications

Since the various promoters enormously increase the intensity of the luminescence, there are certain practical uses for the phenomenon. Among these may be listed qualitative tests for the presence of hydrogen peroxide, especially in the presence of reducing agents (91), and similar tests for the presence of traces of ferrous, cobaltous, and cupric ions, and, with suitable precautions, blood (63, 123, 161, 162).

TABLE 6

Chemiluminescence of various phthalhydrazides

(The substances are arranged in order of decreasing brightness. With the exception of No. 6, all are derivatives of phthalhydrazide (No. 15). The reactions were carried out at 18°C. with hemoglobin as a promoter.)

NO.	PHTHALHYDRAZIDE	NO.	PHTHALHYDRAZIDE
1	5-Amino*† (luminol)	11	6-Acetylamino
2	5-*N*-Methylamino†	12	5,8-Diamino
3	5,8-Diacetylamino†	13	5-Benzoylamino
4	5-Hydroxy‡	14	5-Hydrazino-β-sulfonate
5	5-Hydrazino	15	Phthalhydrazide
6	Pyromellitaz-1,4,6,9-tetraone	16	6,7-Diamino§
7	5-Acetylamino	17	5-Nitro†
8	6-Amino	18	6,7-Dichloro‡
9	5,9-Dichloro	19	6-Nitro
10	5-Chloro	20	For more complex compounds see references 41 and 44.

* A strong shift in the absorption curve maximum in 10 per cent hydrochloric acid (2900 Å.) and in 50 per cent sodium hydroxide (3500 Å.) is attributed to a tautomeric form (196).

† Two maxima in 0.1 *N* sodium hydroxide (196).

‡ One maximum in 0.1 *N* sodium hydroxide (196).

§ Prepared from 6,7-dichlorophthalhydrazide with ammonia and cuprous iodide (46).

D. Luminescence spectra and absorption spectra

The intensity of the luminescence varies with the promoter and with the structure of the phthalhydrazide, and there seems to be some relationship between the luminescence spectra and the corresponding absorption spectra (28, 51, 114); in addition, the fundamental frequencies of bacterial bioluminescence and the chemiluminescence of luminol are identical (49). Table 6 illustrates the order of brightness of various phthalhydrazides as chemiluminescent substances, as well as a few facts regarding the absorption spectra of some of them (46, 196).

E. Effect of substituents on chemiluminescence

Certain generalizations based on the data of table 6 are of some interest. Ortho–para directors ($-I$ effect) increase chemiluminescence in the visible region, while meta directors ($+I$ effect) are weaker and probably have an opposite effect. Favorable groups in the 5- and 8-positions are more effective than in the 6- and 7-positions; and favorable groups in *both* 5- and 8-positions are better than in either alone *except* for the amino group, but the failure in this instance may be due to the highly absorbent character of the red solution. The intensity of luminescence is increased with two hydrazide rings (compound 6) (and the color of the visible light is changed). Finally it should be noted that a change in temperature alters the order of brilliance.

F. Lack of luminescence in five-membered-ring isomers

The five-membered-ring isomers (*N*-aminophthalimides) of these substances have been investigated and found not to exhibit chemiluminescence, but a study of the fluorescent properties revealed that phthalimides and phthalhydrazides containing an amino group ortho to the junction of the two rings (but *not* meta) are fluorescent. *N*-Aminophthalimides, however, are not fluorescent, but *N*-alkylphthalimides are (46).

G. Chemifluorescence

The general phenomenon of chemifluorescence seems to be related to chemiluminescence, and correlation of the two has received some study. The addition of a fluorescing substance (e.g., fluorescein) to a chemiluminescent reaction causes a change of color to that of the fluorescing substance (170) and may intensify the glow in the long-wave part of the spectrum while new absorption maxima appear (88, 115, 116). Luminol itself fluoresces (*cf.* preceding paragraph) at a pH somewhat less than 7 (19), with maximum brilliance at pH = 4.86 (185).

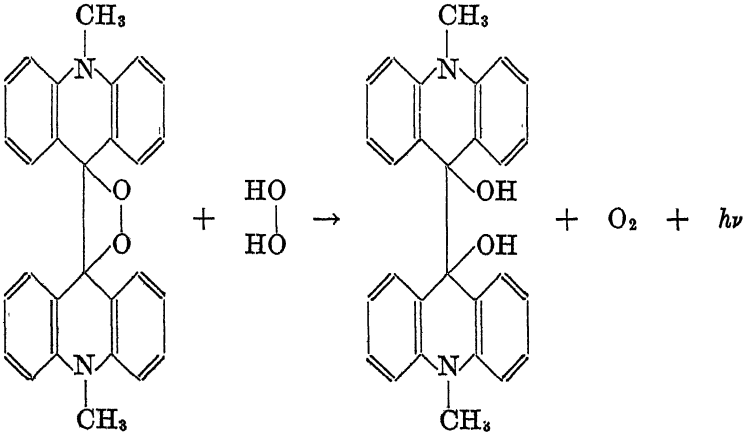
H. Mechanism of chemiluminescence

The problem of a mechanism for the whole process of chemiluminescence in the oxidation of luminol has received considerable attention since the first study by Albrecht (3). A discussion of work in this field up to 1939 is to be found in the papers by Drew (41) and by Weiss (191) in a series on the general subject of chemiluminescence presented to the Faraday Society, and a portion of the following discussion is in part abstracted therefrom.

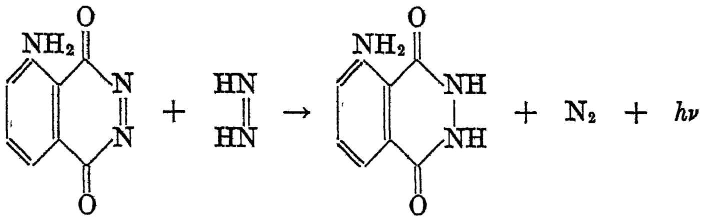
Albrecht (3) first studied the chemiluminescent oxidation of luminol, and the following points constitute a summary of his findings: (*1*) luminol fluoresces (*cf.* above) in acid or neutral solution, the light being bluish (*cf.* 85, 185); (*2*) luminol exhibits a bluish chemiluminescence upon oxidation in alkaline solution; (*3*) many of the usual oxidizing agents produce momentary luminescence; (*4*) a prolonged, though weak, glow is obtained with hydrogen peroxide. This may be intensified (at the expense of the duration: the half-life of the luminescence is approximately the reciprocal of the brilliance (188), and its decay in *the absence* of antioxidants follows a bimolecular law (6)) by catalysts which decompose hydrogen peroxide (hemoglobin, cupric salts, etc.). The luminescence spectrum of luminol (and of 5-acetylaminophthalhydrazide) consists of bands "extending throughout the visible region, with ill-defined maxima at different regions in the blue-green; the fluorescence spectra are not identical with the luminescence spectra, but are similar in character" (41).

A preponderance of evidence has been accumulated (3, 41, 42, 65, 171, 177, 191, 198) purporting to show that the dilactim form of luminol is required for the reaction (i.e., a large excess of alkali must be present, and the phenomenon is not observable with *pure* samples of 2- or 3-alkylated luminols or with 1,4-dimethoxy-5-aminophthalazine). Furthermore the phthalhydrazide structure is essential also, since various isomeric structures do not exhibit chemiluminescence under comparable conditions even though oxidation may occur (46, 80).

It seemed possible to the earlier workers in this field (3, 65, 86) in view of available experimental data that an analogy with the behavior of dimethyldiacridinium salts in the presence of alkaline hydrogen peroxide was possible:

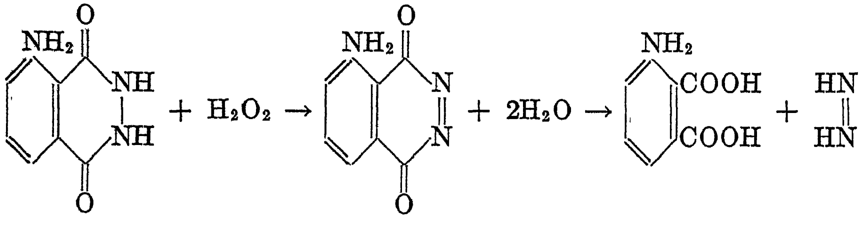


(56a)



(56b)

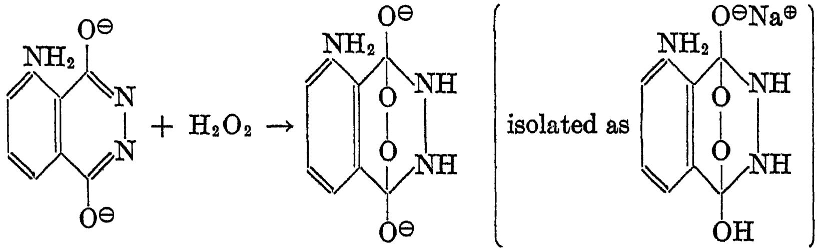
The hypothetical diimide, as well as the azodiacyl compound with which it reacts, arises in a preliminary non-luminescent reaction (3):



(56c)

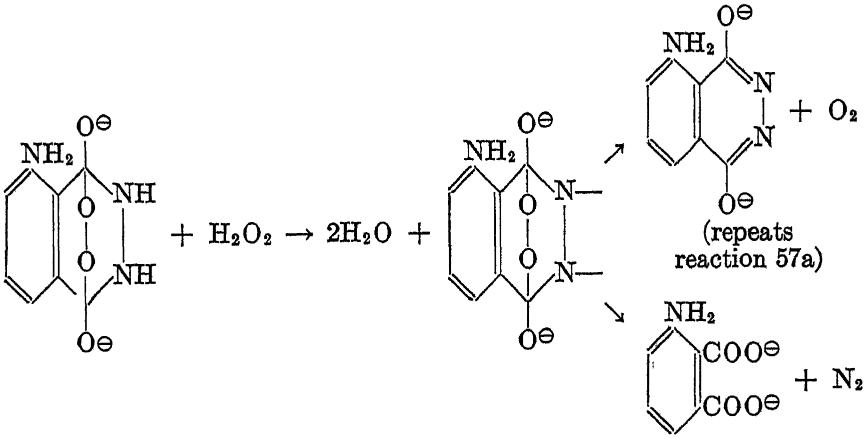
The view that luminol first hydrolyzes and that luminescence is then produced by oxidation of one of the hydrolysis products has been advanced by some workers (167, 168, 196). Without actually specifying the process it may be stated that such a mechanism is controlled by a reaction between the organic compounds and an unstable intermediate formed in the preliminary splitting of the hydrogen peroxide molecule. This hypothesis is flexible, and the rates of increase of initial luminescence with increasing concentration of oxidizable substance, the rates of decay of luminescence with the reaction time of different concentrations (of luminol), and variations in the quantum yield (per mole of hydrogen peroxide[5]) seem to support such a view.

Much of the fundamental exploration of this field was carried out by Drew and his associates, and he has contributed a mechanism which serves as a basis for further experimentation. Drew's mechanism represents something of a departure from the earlier ideas and was first suggested to him by the existence of the conjugated system in the dilactim form of luminol (or of any phthalhydrazide). Having concluded on the basis of experimental data (page 500) that the ion of the dilactim form was required for the reaction, he proposed addition of hydrogen peroxide to this ion as the first step:



(57a)

In subsequent experimental work he was able to isolate both sodium and barium salts of the peroxide ion (43). He then suggested two modes of decomposition, either (or possibly both) being the luminescent reaction, to account for the nature of the final products:



(57b)

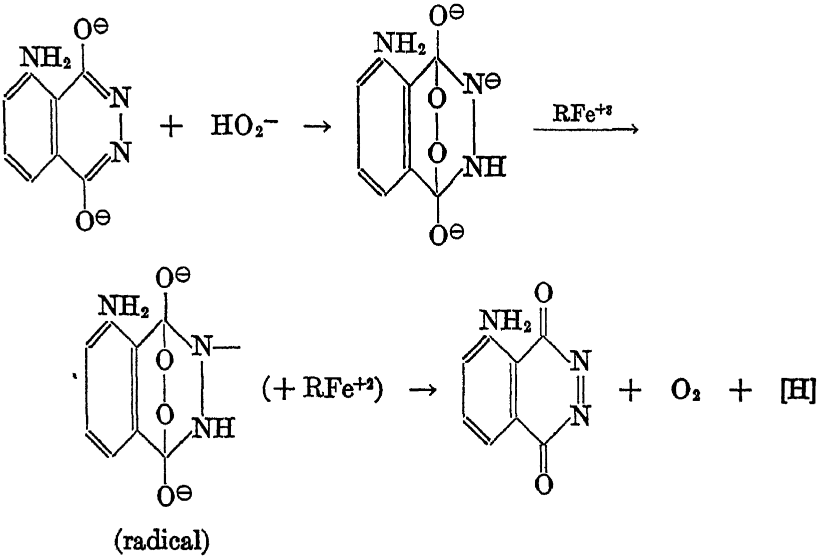
---

[5] The quantum yield of luminescence has been calculated to be 0.3 per cent to 0.5 per cent per mole (73, 181).

In view of the actual isolation of the peroxide salts, this forms a satisfactory basis for further development and has been adopted as such by some investigators (176–178).

A more recent modification of the peroxide mechanism has been advanced by Weber and his associates (185–188) and by Kautsky (86). Weber's mechanism has a distinct advantage over Drew's in that it takes into account the rôle played by the accelerator (e.g., RFe^{+++}) as well as certain other effects. The mechanism may be outlined in six steps as follows, the actual emission of light occurring in the first part of the last step when the activated phthalhydrazide molecule returns to its normal state:

$$H_2O_2 \rightleftharpoons H^+ + HO_2^- \qquad (58a)^6$$

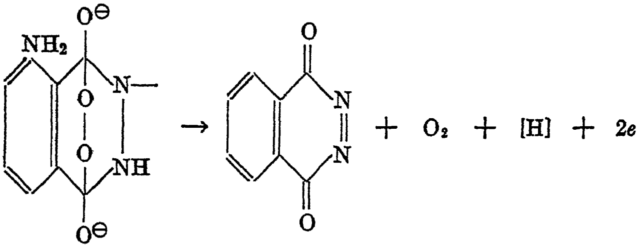


(58b)[6]

$$RFe^{+3} + [H] \rightarrow RFe^{+2} + H^+ \qquad (58c)$$

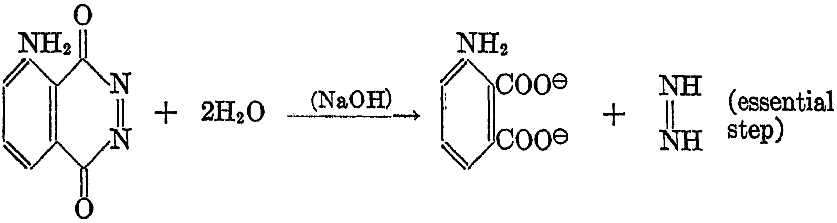
---

[6] The mechanism is presented as described by the original investigators, who evidently overlooked the electron imbalance in equation 58b. To accomplish the last stage in 58b additional oxidizing agent is required thus:

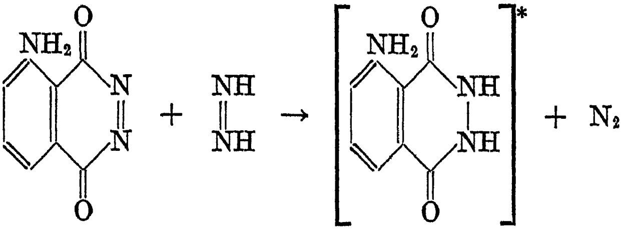


(58b)
(in part)

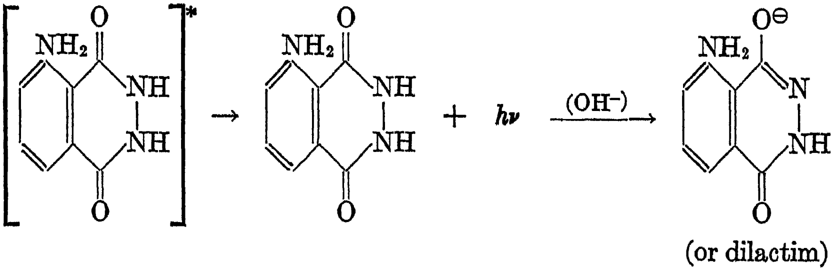
$$3RFe^{+3} + [H] + 2e \rightarrow 3RFe^{+2} + H^+ \qquad (58c)$$



(58d)



(58e)



(58f)

(Kautsky's mechanism appears to be similar once the azodiacyl compound has been formed, but he believes the hydrolysis reaction of equation 58d to be the source of luminescence.)

I. Rôle of the accelerator

The accelerator is invariably altered during the reaction. Its function evidently is to facilitate the formation of the azodiacyl compound (possibly the greenish substance observed by Albrecht (3)) *via* the peroxide ion of Drew, which otherwise must be formed directly from the dilactim ion of luminol by the loss of two electrons. If the *reduced* accelerator is readily reoxidizable by oxygen (hemoglobin, for example),

$$\mathrm{RFe^{+2}} \xrightarrow{O_2} \mathrm{RFe^{+3}}$$

its function is purely that of a catalyst. On the other hand, if such reoxidation is difficult, the accelerator is a reactant (ferritin, for example). Weber also noted that all accelerators are irreversibly changed in the reaction, and that this change is the rate-determining step.

J. Quenching effect of excess alkali

Finally, Weber holds that the quenching effect of too great an excess of alkali may be due to a resultant speeding up of the final enolization process (last part of equation 58f) to a point where it occurs more rapidly than emission; and since only the dicarbonyl form of luminol fluoresces (185; *cf.* 85), any change in pH tending to promote very rapid lactimization would destroy the essential activated dicarbonyl form of luminol faster than the latter could give up its excess energy as luminescence. Obviously, since the dilactim ion seems to be required for the initial formation of the peroxide, a fine balance must be struck between enough alkalinity for this reaction and too great alkalinity for chemiluminescence. In addition, any significant increase in pH will change the oxidation–reduction potential of the accelerators. Weber concludes with a study of the kinetics of the reaction which give good support to his mechanism, which thus far seems to be the most satisfactory one. However, the problem should in no manner be regarded as solved.

XI. USES OF PHTHALAZINES, PHTHALAZONES, AND PHTHALHYDRAZIDES

The preparation of various phthalazines and of phthalazones has often proven a satisfactory means of obtaining stable crystalline derivatives of *o*-dicarbonyl aromatic compounds and of *o*-carbonyl aromatic carboxylic acids, respectively. Certain mercaptophthalazines have been suggested and patented as rubber accelerators (4). Luminol finds application in the qualitative determination of minute quantities of various ions and of blood (63, 91, 123, 161, 162), and also serves as a readily available reagent for the study and demonstration of the phenomena of chemiluminescence and chemifluorescence. The study of the synthesis of other phthalhydrazides has contributed to these latter studies, since Drew has observed a correlation between the tendency toward phthalhydrazide formation as opposed to the formation of the isomeric *N*-aminophthalimides and the intensity of chemiluminescence (41).

Finally, some phthalazones and phthalhydrazides have been investigated for various physiological or pharmaceutical purposes (9, 40, 85) or as surface-active agents (78); but by far the greater bulk of research in the general field of phthalazine chemistry has been of a purely fundamental character.

XII. REFERENCES

(1) Aggarwal, J. S., Darbari, N. L., and Ray, J. N.: J. Chem. Soc. **1929**, 1941.
(2) Aggarwal, J. S., Khera, I. D., and Ray, J. N.: J. Chem. Soc. **1930**, 2354.
(3) Albrecht, H. O.: Z. physik. Chem. **136**, 321 (1928).
(4) Armstrong, R. T.: U. S. patent 2,382,769 (August 14, 1945).
(5) Badger, G. M.: J. Chem. Soc. **1941**, 351.
(6) Baur, E.: Helv. Chim. Acta **23**, 449 (1940).
(7) Bethmann, F.: Ber. **32**, 1104 (1899).
(8) Biquard, D., and Grammaticakis, P.: Bull. soc. chim. [5] **9**, 675 (1942).
(9) Blanksma, J. J., and Bakels, H. A.: Rec. trav. chim. **58**, 497 (1939).
(10) Blicke, F. F., and Swisher, R. D.: J. Am. Chem. Soc. **56**, 923 (1934).
(11) Blicke, F. F., and Weinkauff, O. J.: J. Am. Chem. Soc. **54**, 1454 (1932).
(12) Bogert, M. T., and Boroscheck, L.: J. Am. Chem. Soc. **23**, 750 (1901).
(13) Borsche, W., and Diacont, K.: Ann. **510**, 287 (1934).
(14) Borsche, W., Diacont, K., and Hanau, H.: Ber. **67B**, 675 (1934).
(15) Borsche, W., and Heimbürger, G.: Ber **48**, 966 (1915).
(16) Bradsher, C. K., and Smith, E. S.: J. Am. Chem. Soc. **65**, 854 (1943).

Bradsher, C. K., and Wissow, L. J.: J. Am. Chem. Soc. **68**, 1094 (1946).
Bradsher, C. K., Rapoport, L., and Anderson, P.: J. Am. Chem. Soc. **68**, 2152 (1946).
Cf. Berliner, E.: J. Am. Chem. Soc. **64**, 2894 (1943) and Newman, M. S.: J. Am. Chem. Soc. **64**, 2324 (1943).
(17) Bresler, S. E.: Acta Physicochim. U.R.S.S. **12**, 323 (1940).
(18) Briner, E.: Helv. Chim. Acta **23**, 320 (1940).
(19) Briner, E., and Perrottet, E.: Helv. Chim. Acta **23**, 1253 (1940).
(20) Bromberg, O.: Ber. **29**, 1434 (1896).
(21) Bülow, C., and Deseniss, M.: Ber **39**, 2275 (1906).
(22) Buu-Hoï: Bull. soc. chim. [5] **9**, 351 (1942).
(23) Chapman, A. W.: J. Chem. Soc. **1927**, 1743.
(24) Chattaway, F. D., and Tesh, W.: J. Chem. Soc. **117**, 711 (1920).
(25) Clar, E., John, F., and Hawran, B.: Ber. **62B**, 940 (1929).
(26) Cook, A. H.: J. Chem. Soc. **1938**, 1845.
(27) Cornillot, A.: Ann. chim. [10] **8**, 120 (1927).
(28) Cottman, E. W.: Proc. Indiana Acad. Sci. **49**, 115 (1939).
(29) Curtius, T.: J. prakt. Chem. [2] **50**, 275 (1894).
(30) Curtius, T., and Davidis, E.: J. prakt. Chem. [2] **54**, 66 (1896).
(31) Curtius, T., and Foersterling, H. A.: J. prakt. Chem. [2] **51**, 371 (1895).
(32) Curtius, T., and Hoesch, A.: J. prakt. Chem. [2] **76**, 301 (1908).
(33) Curtius, T., and Semper, A.: Ber. **46**, 1162 (1913).
(34) Darapsky, A., and Heinricks, P.: J. prakt. Chem. **146**, 307 (1936).
(35) Daube, A.: Ber. **38**, 206 (1905).
(36) Déribéré, M.: Tech. moderne **30**, 489 (1938); **31**, 256 (1939); **32**, 10 (1940).
(37) Dieckmann, W., and Meiser, W.: Ber. **41**, 3253 (1909).
(38) Dischendorfer, O.: Monatsh. **50**, 97 (1928).
(39) Dischendorfer, O.: Monatsh. **66**, 201 (1935).
(40) Drake, N. L., and Peck, R. M.: J. Am. Chem. Soc. **68**, 1313 (1946).
(41) Drew, H. D. K.: Trans. Faraday Soc. **35**, 207 (1939).
(42) Drew, H. D. K., and Garwood, R. F.: J. Chem. Soc. **1937**, 1841.
(43) Drew, H. D. K., and Garwood, R. F.: J. Chem. Soc. **1938**, 791.
(44) Drew, H. D. K., and Garwood, R. F.: J. Chem. Soc. **1939**, 836.
(45) Drew, H. D. K., and Hatt, H. H.: J. Chem. Soc. **1937**, 16.
Drew, H. D. K., and Pearman, F. H.: J. Chem. Soc. **1937**, 26.
Drew, H. D. K., Hatt, H. H., and Hobart, F. A.: J. Chem. Soc. **1937**, 33.
(46) Drew, H. D. K., and Pearman, F. H.: J. Chem. Soc. **1937**, 586.
(47) Dunlap, F. L.: J. Am. Chem. Soc. **27**, 1091 (1905).
(48) Dziewonski, K., and Loewenhof, A.: Bull. intern. acad. polon. sci. 521 (1927A).
(49) Eymers, G. J., and van Schouwenburg, K. L.: Enzymologia **1**, 107 (1936).
(50) Fargher, R. G., and Perkin, W. H., Jr.: J. Chem. Soc. **119**, 1724 (1921).
(51) Feofilov, P. P.: Bull. acad. sci. U.R.S.S., Sér. phys. **9**, 317 (1945).
(52) Fieser, L. F., and Lothrop, W. C.: J. Am. Chem. Soc. **58**, 2050 (1936); **59**, 945 (1937).
(53) Flosdorf, E. W., Chambers, L. A., and Malisoff, W. M.: J. Am. Chem. Soc. **58**, 1069 (1936).
(54) Frank, R. L., Eklund, H., Richter, J. W., Vanneman, C. R., and Wennerberg, A. N.: J. Am. Chem. Soc. **66**, 1 (1944).
(55) Fränkel, K.: Ber. **33**, 2808 (1900).
(56) Freund, M., and Fleischer, K.: Ann. **409**, 268 (1915).
(57) Gabriel, S.: Ber. **36**, 3373 (1903).
(58) Gabriel, S.: Ber. **40**, 71 (1907).
(59) Gabriel, S., and Eschenbach, G.: Ber. **30**, 3022 (1897).
(60) Gabriel, S., and Müller, F.: Ber. **28**, 1830 (1895).
(61) Gabriel, S., and Neumann, A.: Ber. **26**, 521, 705 (1893).
(62) Gabriel, S., and Pinkus, G.: Ber. **26**, 2210 (1893).

(63) Geyer, B. P., and Smith, G. M.: J. Am. Chem. Soc. **63**, 3071 (1941).
(64) Gheorghiu, G.: Bull. soc. chim. [4] **53**, 151 (1933).
(65) Gleu, K., and Petsch, W.: Angew. Chem. **48**, 57 (1935).
(66) Gleu, K., and Pfannstiel, K.: J. prakt. Chem. **146**, 137 (1936).
(67) Glogau, A.: Monatsh. **25**, 391 (1904).
(68) Graenacher, C., Ackermann, F., and Bruengger, H.: U. S. patent 2,235,480 (March 18, 1941).
(69) Guyot, A., and Pignet, P.: Compt. rend. **146**, 984 (1908).
(70) Guyot, A., and Valette, F.: Ann. chim. phys. [8] **23**, 363 (1910).
(71) Hammett, L. P.: *Physical Organic Chemistry*, pp. 333, 357. McGraw-Hill Book Company, Inc., New York (1940).
(72) Reference 71, pp. 317–28.
(73) Harris, L., and Parker, A. S.: J. Am. Chem. Soc. **57**, 1939 (1935).
(74) Harvey, E. N.: J. Phys. Chem. **33**, 1456 (1929).
(75) Hatt, H. H., and Stephenson, E. F. M.: J. Chem. Soc. **1943**, 658.
(76) Heller, G., Buchwaldt, A., Fuchs, R., Kleinicke, W., and Kloss, J.: J. prakt. Chem. **111**, 1 (1925).
(77) Henriques, R.: Ber. **21**, 1607 (1888).
(78) Hentrich, W., and Schirm, E.: U. S. patent 2,394,306 (February 5, 1946).
(79) Hötte, B.: J. prakt. Chem. [2] **33**, 99 (1886); **35**, 265 (1887).
(80) Huntress, E. H., and Gladding, J. V. K.: J. Am. Chem. Soc. **64**, 2644 (1942).
(81) Huntress, E. H., Stanley, L. N., and Parker, A. S.: J. Am. Chem. Soc. **56**, 241 (1934).
(82) Huntress, E. H., Stanley, L. N., and Parker, A. S.: J. Chem. Education **11**, 142 (1934).
(83) Kaiser, J.: Ann. **257**, 95 (1890).
(84) Kaufmann, H. P.: Z. angew. Chem. **40**, 69 (1927).
(85) Kautsky, H., and Hohn, H.: Kolloid-Z. **75**, 164 (1936).
(86) Kautsky, H., and Kaiser, K. H.: Naturwissenschaften **30**, 148 (1942).
(87) Kipping, F. B., and Mann, F. G.: J. Chem. Soc. **1927**, 528.
(88) Kubal, J.: Phot. Korr. **74**, 132 (1938).
(89) Kuhn, R., Winterstein, A., and Balser, G.: Ber. **63B**, 3178 (1930).
(90) Kuroda, C., and Perkin, W. H., Jr.: J. Chem. Soc. **123**, 2094 (1923).
(91) Langenbeck, W., and Ruge, U.: Ber. **70B**, 367 (1937).
(92) Liebermann, C.: Ber. **19**, 763 (1886).
(93) Liebermann, C., and Bistrzycki, A.: Ber. **26**, 531 (1893).
(94) Lieck, A.: Ber. **38**, 3918 (1905).
(95) Marriott, G. J., and Robinson, R.: J. Chem. Soc. **1939**, 134.
(96) Meran, G.: Ann. sci. univ. Jassy (I) **27**, 27 (1941).
(97) Meyer, H.: Monatsh. **25**, 1177 (1904).
(98) Meyer, H.: Monatsh. **28**, 1211 (1907).
(99) Meyer, H., and Turnau, R.: Monatsh. **30**, 483 (1909).
(100) Mihăilescu, M., and Florescu, L.: Bull. sec. sci. acad. Roumaine **8**, 303 (1923). Mihăilescu, M., and Protopescu, L.: Bul. soc. chim. România **12**, 95 (1930).
(101) Mills, W. H., and Nixon, I. G.: J. Chem. Soc. **1930**, 2510.
(102) Mitter, P. C., and Sen. J. N.: J. Chem. Soc. **111**, 988 (1917).
(103) Mitter, P. G., and Sen, J. N.: J. Chem. Soc. **115**, 1145 (1919).
(104) Morton, A. A.: *The Chemistry of Heterocyclic Compounds*, pp. 391, 506. McGraw-Hill Book Company, Inc., New York (1946).
(105) Mumm, O., Hesse, H., and Volquartz, H.: Ber. **48**, 379 (1915).
(105) Noguchi, T., and Kawanami, M.: J. Pharm. Soc. Japan **57**, 196 (1937).
(107) Olivero, A.: Gazz. chim. ital. **64**, 139 (1934).
(108) Orndorff, W. R., and Kline, E.: J. Am. Chem. Soc. **46**, 2276 (1924).
(109) Padoa, M.: Atti acad. Lincei [5] **12, I**, 393 (1903).

(110) Paul, V.: Ber. **32**, 2014 (1899).
(111) Pellizzari, G.: Gazz. chim. ital. **16**, 200 (1886).
(112) Perkin, W. H., Jr., and Stone, J. F. S.: J. Chem. Soc. **127**, 2275 (1925).
(113) Phelps, I. K.: Am. Chem. J. **33**, 586 (1905).
(114) Plotnikov, I.: Phot. Korr. **75**, 89 (1939).
(115) Plotnikov, I., Doljak, M., and Kopsič, T.: Phot. Korr. **76**, 43 (1940).
(116) Plotnikov, I., and Kubal, J.: Phot. Korr. **74**, 97 (1938).
(117) Racine, S.: Ann. **239**, 78 (1887).
(118) Rădulescu, D.: Bul. soc. chim. România **8**, 117 (1926).
(119) Rădulescu, D.: Bul. soc. chim. România **12**, 137 (1930).
(120) Rădulescu, D., and Alexa, V.: Z. physik. Chem. **B8**, 382 (1930).
(121) Rădulescu, D., and Alexa, V.: Bul. soc. chim. România **12**, 140 (1930).
(122) Rădulescu, D., and Georgescu, V.: Bull. soc. chim. [4] **37**, 881 (1925).
(123) Richter, O.: Radiologica **1**, 50 (1937).
(124) Richter, O.: Fundamenta Radiol. **4**, 141 (1939).
(125) Roser, W.: Ber. **18**, 802 (1885).
(126) Roser, W.: Ann. **282**, 363 (1894).
(127) Rowe, F. M., Adams, D. A. W., Peters, A. T., and Gillam, A. E.: J. Chem. Soc. **1937**, 90.
(128) Rowe, F. M., Dovey, W. C., Garforth, B., Levin, E., Pask, J. D., and Peters, A. T.: J. Chem. Soc. **1935**, 1796.
(129) Rowe, F. M., and Dunbar, C.: J. Chem. Soc. **1932**, 11.
(130) Rowe, F. M., Dunbar, C., and Williams, N. H.: J. Chem. Soc. **1931**, 1073.
(131) Rowe, F. M., Gillan, J. G., and Peters, A. T.: J. Chem. Soc. **1935**, 1808.
(132) Rowe, F. M., Haigh, A. S., and Peters, A. T.: J. Chem. Soc. **1936**, 1098.
(133) Rowe, F. M., Heath, G. M., and Patel, C. V.: J. Chem. Soc. **1936**, 311.
(134) Rowe, F. M., Himmat, M. A., and Levin, E.: J. Chem. Soc. **1928**, 2556.
(135) Rowe, F. M., Jambuserwala, G. B., and Partridge, H. W.: J. Chem. Soc. **1935**, 1134.
(136) Rowe, F. M., Lecutier, M. A., and Peters, A. T.: J. Chem. Soc. **1938**, 1079.
(137) Rowe, F. M., and Levin, E.: J. Chem. Soc. **1928**, 2550.
(138) Rowe, F. M., Levin, E., Burns, A. C., Davies, J. S. H., and Tepper, W.: J. Chem. Soc. **1926**, 690.
(139) Rowe, F. M., and Peters, A. T.: J. Chem. Soc. **1931**, 1067.
(140) Rowe, F. M., and Peters, A. T.: J. Chem. Soc. **1931**, 1918.
(141) Rowe, F. M., and Peters, A. T.: J. Chem. Soc. **1933**, 1067 (*cf.* Ann. Repts. on Progress Chem. (Chem. Soc. London) **28**, 122 (1931)).
(142) Rowe, F. M., and Peters, A. T.: J. Chem. Soc. **1933**, 1331.
(143) Rowe, F. M., and Siddle, F. J.: J. Chem. Soc. **1932**, 473.
(144) Rowe, F. M., and Tomlinson, F. S.: J. Chem. Soc. **1932**, 1118.
(145) Rowe, F. M., and Twitchett, H. J.: J. Chem. Soc. **1936**, 1704.
(146) Ruggli, P., and Meyer, R. E.: Helv. Chim. Acta **5**, 28 (1922).
(147) Ruggli, P., and Zickendraht, C.: Helv. Chim. Acta **28**, 1377 (1945).
(148) Schales, O.: Ber. **71B**, 447 (1938).
(149) Schales, O.: Ber. **72B**, 167 (1939).
(150) Schneider, E.: J. Am. Chem. Soc. **63**, 1477 (1941).
(151) Scholl, R., and Neumann, H.: Ber. **55B**, 118 (1922).
(152) Schöpff, M.: Ber. **26**, 1121 (1893).
(153) Seekles, L.: Rec. trav. chim. **43**, 329 (1924).
(154) Seer, C., and Dischendorfer, O.: Monatsh. **34**, 1493 (1913).
(155) Seidel, F., and Bezner, O.: Ber. **65B**, 1566 (1932).
(156) Sernagiotto, E., and Paravagno, M. D.: Gazz. chim. ital. **44**, **I**, 538 (1914).
(157) Sidgwick, N. V.: J. Chem. Soc. **107**, 672 (1915).

(158) Sidgwick, N. V. (Taylor, T. W. J., and Baker, W.): *The Organic Chemistry of Nitrogen*, pp. 495–6. University Press, Oxford (1937).
(159) Reference 158, Chapter 18.
(160) Smith, P. A. S.: "The Curtius Reaction" in *Organic Reactions* (Roger Adams, *Editor-in-Chief*), Vol. III, Chap. 9. John Wiley and Sons, Inc., New York (1946).
(161) Steigmann, A.: Chemistry & Industry **1941,** 889.
(162) Steigmann, A.: J. Soc. Chem. Ind. **61,** 36 (1942).
(163) Stephenson, E. F. M.: J. Chem. Soc. **1944,** 678.
(164) Stevens, T. S., Creighton, E. M., Gordon, A. B., and MacNicol, M.: J. Chem. Soc. **1928,** 3193.
Stevens, T. S.: J. Chem. Soc. **1930,** 2107.
Stevens, T. S., Shedden, W. W., Stiller, E. T., and Thomson, T.: J. Chem. Soc. **1930,** 2119.
Thomson, T., and Stevens, T. S.: J. Chem. Soc. **1932,** 55.
Dunn, J. L., and Stevens, T. S.: J. Chem. Soc. **1932,** 1926.
(165) Stollé, R., and Storch, H.: J. prakt. Chem. **135,** 128 (1932).
(166) Stross, F. H., and Branch, G. E. K.: J. Org. Chem. **3,** 385 (1938).
(167) Sveshnikov, B. Y.: Acta Physicochim. U.R.S.S. **8,** 441 (1938); J. Phys. Chem. (U.S.S.R.) **11,** 720 (1938).
(168) Sveshnikov, B. Y.: Compt. rend. acad. sci. U.R.S.S. **35,** 278 (1942).
(169) Tamamushi, B.: Naturwissenschaften **25,** 318 (1937).
(170) Tamamushi, B.: Naturwissenschaften **28,** 722 (1940).
(171) Tamamushi, B., and Akiyama, H.: Z. physik. Chem. **B38,** 400 (1937).
(172) Teppema, J.: Rec. trav. chim. **42,** 30 (1923).
(173) Thiele, J., and Falk, K. G.: Ann. **347,** 112 (1906).
(174) Thielert, H., and Pfeiffer, P.: Ber. **71B,** 1399 (1938).
(175) Tust, K.: Ber. **25,** 1995 (1892).
(176) Vasserman, E. S.: Compt. rend. acad. sci. U.R.S.S. **24,** 704 (1939).
(177) Vasserman, E. S., and Miklukhin, G. P.: J. Gen Chem. (U.S.S.R.) **9,** 606 (1939).
(178) Vasserman, E. S., and Miklukhin, G. P.: J. Gen. Chem. (U.S.S.R.) **10,** 202 (1940).
(179) Vaughan, W. R.: Unpublished observation.
(180) Vaughan, W. R., and Baird, S. L., Jr.: J. Am. Chem. Soc. **68,** 1314 (1946).
(181) Vészi, G.: Technikai Kurir **8** [2], 1, 7 (1937).
(182) von Braun, J., Braunsdorf, O., Engelbertz, P., Hahn, E., Hahn, G., Hainbach, O., Kredel, W., and Larbig, K.: Ber. **56B,** 2332 (1923).
(183) von Rothenburg, R.: Ber. **27,** 691 (1894).
(184) von Rothenburg, R.: J. prakt. Chem. [2] **51,** 140 (1895).
(185) Weber, K.: Ber. **75B,** 565 (1942).
(186) Weber, K., and Krajčinović, M.: Ber. **75B,** 2051 (1942).
(187) Weber, K., Lahm, W., and Hieber, E.: Ber. **76B,** 366 (1943).
(188) Weber, K., Režek, A., and Vouk, V.: Ber. **75B,** 1141 (1942).
(189) Wegler, R.: J. prakt. Chem. **148,** 135 (1937).
(190) Weiss, J.: Trans. Faraday Soc. **35,** 219 (1939).
(191) Weiss, R., and Kratz, S. R.: Monatsh. **50,** 429 (1928).
(192) Wislicenus, W., and Neber, P.: Ann. **418,** 274 (1919).
(193) Witte, A. A. M.: Rec. trav. chim. **54,** 471 (1935).
(194) Wölbing, H.: Ber. **38,** 3925 (1905).
(195) Wolfram, A.: German patent 481,650 (July 17, 1925).
(196) Zelinskiĭ, V. V., and Sveshnikov, B. Y.: Compt. rend. acad. sci. U.R.S.S. **34,** 252 (1942).
(197) Zellner, C. N., and Dougherty, G.: J. Am. Chem. Soc. **58,** 1811 (1936).
(198) Zellner, C. N., and Dougherty, G.: J. Am. Chem. Soc. **59,** 2580 (1937).

THE CHEMISTRY OF SPIROPYRANS

AHMED MUSTAFA

Department of Chemistry, Faculty of Science, University Fouad I, Cairo, Egypt

Received March 15, 1948

CONTENTS

I. Introduction 509
II. Methods of preparation 509
  A. Spiropyrans derived from aliphatic ketones 509
    (1) Acetone and aliphatic analogues 509
    (2) β-Phenethyl methyl ketone 510
    (3) Acetoacetate derivatives and acetonedicarboxylic ethyl ester 512
    (4) Cyclic ketones 512
    (5) Dibenzyl ketone 513
  B. Spiropyrans derived from 9-methyl- and 9-ethyl-xanthylinium salts 513
  C. Spiropyrans derived from substituted chromones 513
  D. Isospiropyrans 514
III. Chemical properties 514
  A. Action with acids 514
  B. Action with alkalies 514
  C. Action with Grignard reagents 514
IV. Color phenomena associated with spiropyrans 519
V. References 522

I. INTRODUCTION

Whereas dibenzospiropyrans (XXI) (1, 2) were synthesized many years ago, substituted products of XXI (5, 16), benzo-α-naphthospiropyran (XXXI) (11), benzo-β-naphthospiropyran (XXII) (4, 9, 12), di-β-naphthospiropyran (XXIII) (3, 4, 5, 8, 11, 12), α,β-dinaphthospiropyran (XXIV) (11, 12), benzoxanthospiropyran (XXX) (15), xantho-β-naphthospiropyran (XXIX) (15), and benzo-β-naphthoisospiropyran (XXV) (10, 11, 13) have been only recently prepared. The present review summarizes the methods of preparation and chemical properties of these compounds. A discussion of the theories concerning their color phenomena is also given.

II. METHODS OF PREPARATION

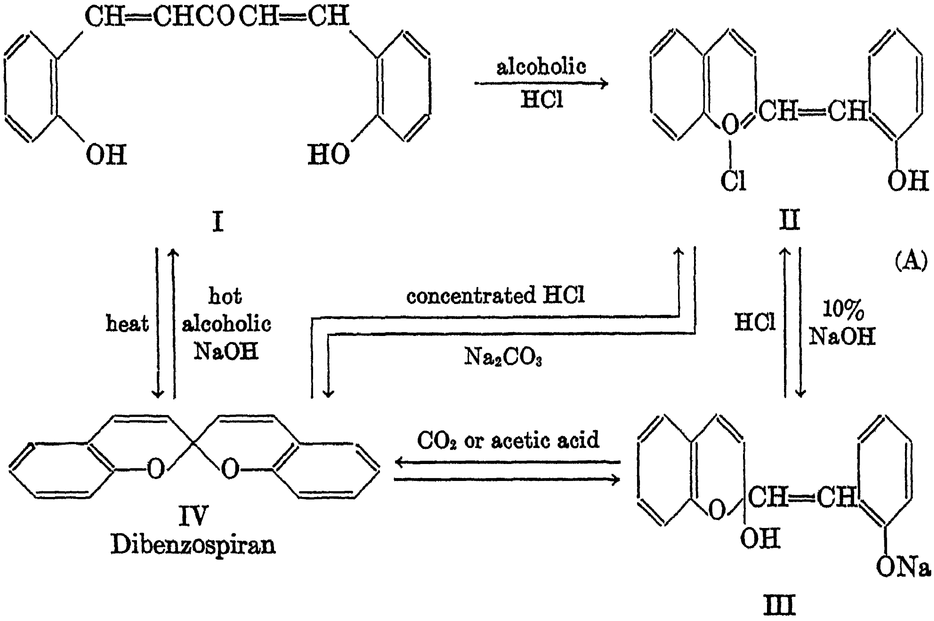
The general method for the preparation of spiropyrans consists in hydrolyzing the synthesized benzo- or naphtho-pyrylium salts. The condensation of salicylaldehyde, or of 2-naphthol-1-aldehyde and substances of analogous structure in an acid medium, with an aliphatic or aromatic ketone containing an acidic methylene group next to the carbonyl (1) leads to the formation of pyrylium salts which on treatment with ammonia give substituted spiropyrans.

A. Spiropyrans derived from aliphatic ketones

(1) Acetone and aliphatic analogues

Decker and Felser (2) obtained the sodium salt of 2-*o*-hydroxystyrylbenzopyranol (III) by the action of 10 per cent aqueous sodium hydroxide solution on

2-*o*-hydroxystyrylbenzopyrylium chloride (II), which was prepared by the action of alcoholic hydrogen chloride on the condensation product (I) obtained from salicylaldehyde and acetone. When the sodium salt was treated with carbon dioxide or acetic acid, dibenzospiropyran (IV) was obtained (compare scheme A).

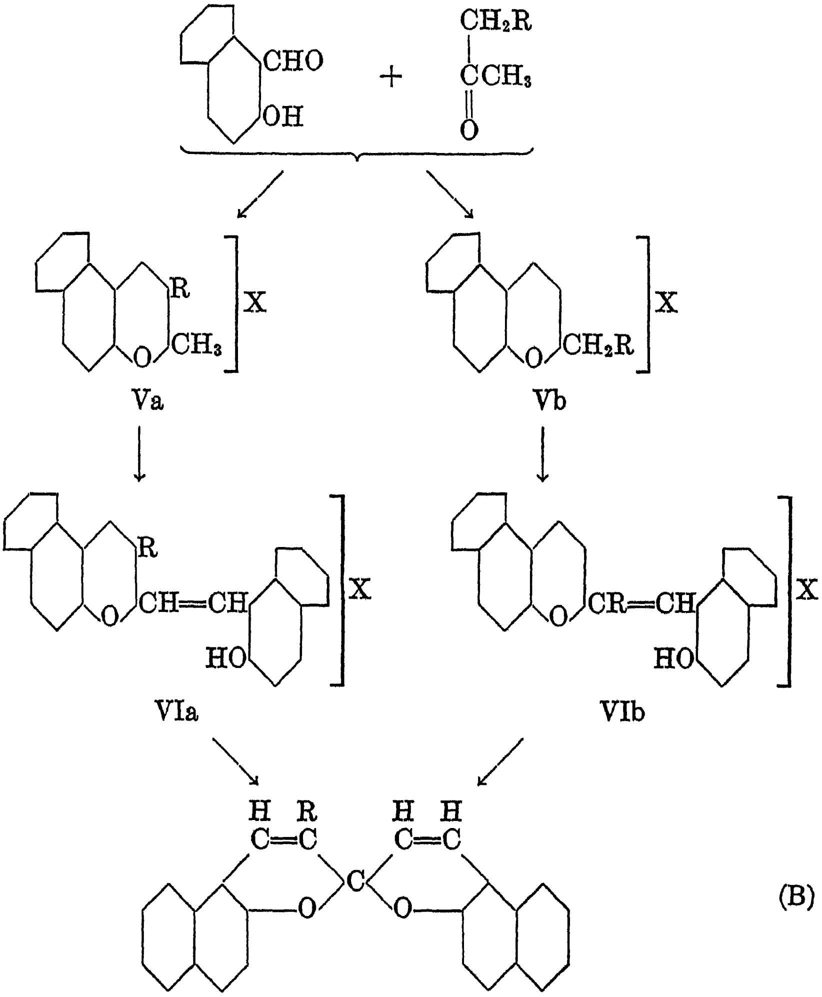


Dilthey and Wizinger (6) proved that the reaction between the *o*-hydroxyaldehyde and the acetone derivatives takes place (using a condensing agent of an acidic nature) in two stages. The intermediate product, e.g., α-methylbenzopyrylium salt (Va or Vb), for which two constitutions (compare scheme B) are possible, may be isolated and used in preparing asymmetrically substituted spiropyrans by treatment with different aldehydes.

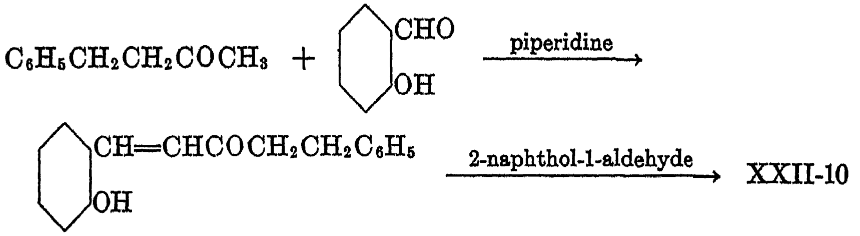
The salt of the type VI (*o*-hydroxystyrylbenzopyrylium salt) can be isolated even if the components are allowed to react in molecular proportions (1:1). Examples of ethyl methyl ketone with salicylaldehyde and 2-naphthol-1-aldehyde and their corresponding spiropyrans are quoted. The corresponding di-β-naphthospiropyrans (XXIII) have been successively prepared (3, 14).

(2) β-Phenethyl methyl ketone

Heilbron and coworkers (9) have stated that the methyl and not the methylene group is reactive in the case of β-phenethyl methyl ketone in the presence of piperidine. Thus, β-phenethyl methyl ketone condenses with salicylaldehyde in the presence of piperidine, yielding an unsaturated ketone (VII) which, when further condensed with 2-naphthol-1-aldehyde, leads to 3′-benzyl-β-naphthospiropyran (XXII-10) (compare scheme C).

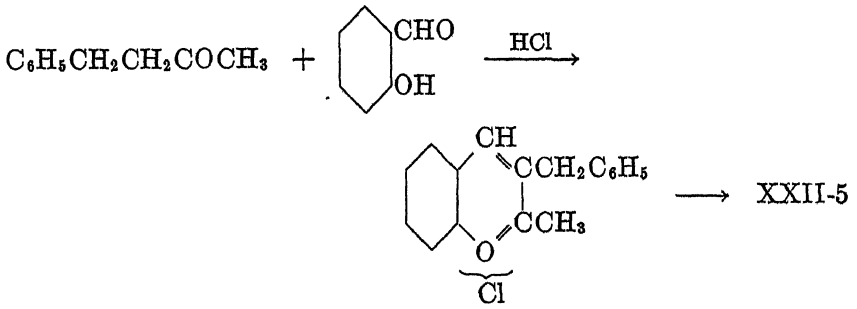


(B)



(C)

The same result is obtained when sodium hydroxide is employed in place of piperidine; when the condensation is carried out with hydrochloric acid, salicylaldehyde and β-phenethyl methyl ketone give a different product as a result of the methylene group entering into the reaction. Thus the pyrylium salt (VIII) formed reacts with 2-naphthol-1-aldehyde, yielding 3-benzylbenzo-β-naphthospiropyran (XXII-5) (compare scheme D).

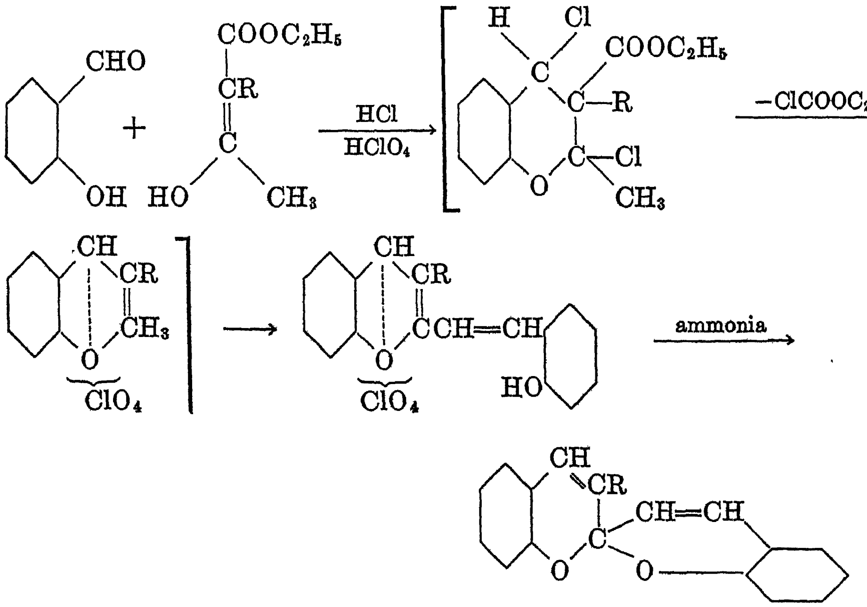


VIII

(D)

(3) Acetoacetate derivatives and acetonedicarboxylic ethyl ester

Löwenbein and Katz (16) obtained 3-methyldibenzospiropyran (XXI-2) by the action of ethyl α-methylacetoacetate on salicylaldehyde in ethereal solution in the presence of hydrochloric acid and perchloric acid, followed by treatment of the 2-*o*-hydroxystyryl-3-methylbenzopyrylium perchlorate formed with ammonia (compare scheme E).



(E)

Similarly, ethyl or methyl benzylacetoacetate and salicylaldehyde yield 3-benzyldibenzospiropyran (XXI-3), and with 2-naphthol-1-aldehyde, 3-benzyldinaphthospiropyran (XXIII-5) is obtained. Dickinson and Heilbron (4), using ethyl acetonedicarboxylate, obtained ethyl di-β-naphthospiropyran-3,3′-dicarboxylate (XXIII-10).

(4) Cyclic ketones

3,3′-Dimethylene- (XXVI) and 3,3′-tetramethylene-di-β-naphthospiropyran (XXVIII) were prepared, respectively, by condensing cyclopentanone and cycloheptanone with 2-naphthol-1-aldehyde in the presence of hydrogen chloride, followed by hydrolysis of the resultant pyrylium salt (11). In the case of cyclohexanone, 3,3′-trimethylenedi-β-naphthospiropyran (XXVII) was obtained (8).

(5) Dibenzyl ketone

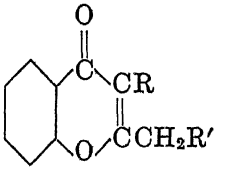
The condensation of 2-naphthol-1-aldehyde with dibenzyl ketone (8) has been studied by Heilbron and coworkers (5). 3,3′-Diphenyldibenzospiropyran (XXI-4) is obtained by condensing two molecules of salicylaldehyde with one molecule of dibenzyl ketone (5).

B. Spiropyrans derived from 9-methyl- and 9-ethyl-xanthylinium salts

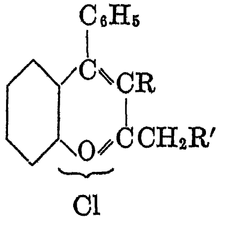
Xantho-β-naphthospiropyran (XXIX) is obtained by the condensation of methylxanthenol and 2-naphthol-1-aldehyde in the presence of hydrogen chloride gas. In the case of salicylaldehyde, benzoxanthospiropyran (XXX) is obtained (15).

C. Spiropyrans derived from substituted chromones

The general method for the preparation of spiropyrans consists in converting the appropriate *o*-hydroxyphenyl ketone into the chromone (IX) from which the pyrylium salt (X) is obtained when treated with phenylmagnesium bromide, followed by decomposition with concentrated hydrochloric acid. Condensation of X with 2-naphthol-1-aldehyde yields the naphthovinylpyrylium salt, from which the corresponding spiropyran results on hydrolysis, e.g.:



IX



X

4-Phenyl-3′-methylbenzo-β-naphthospiropyran (XXII-12) (12) is obtained from 2-ethylchromone (IX: $R = H$, $R' = CH_3$) when treated with phenylmagnesium bromide, forming 4-phenyl-2-ethylbenzopyrylium chloride (X: $R = H$; $R' = CH_3$) as mentioned above.

On the other hand, when 2-ethyl-α-naphtho-γ-pyrone and 3-methyl-2-ethyl-α-naphtho-γ-pyrone (the terms naphtho-α-pyrone and naphtho-γ-pyrone are used in place of naphthocoumarin and naphthochromone, respectively (12)), they give rise to the new series of α,β-dinaphthospiropyrans, e.g., 4-phenyl-3′-methyl-α,β-dinaphthospiropyran (XXIV-1) and 4-phenyl-3,3′-dimethyl-α,β-dinaphthospiropyran (XXIV-4) (11, 12).

Similarly, when 4-phenyl-2,3-dimethyl-α-naphthopyrylium perchlorate was condensed with salicylaldehyde, followed by hydrolysis, 4′-phenyl-3′-methylbenzo-α-naphthospiropyran (XXXI) was obtained (11).

D. Isospiropyrans

The substitution of coumarin derivatives for chromone derivatives in the preparation of spiropyrans leads to the formation of the corresponding isospiropyrans (XXV). 7-Methoxy-2-phenyl-3,4-dimethylcoumarin, when treated with phenylmagnesium bromide as usual, yields 7-methoxy-2-phenyl-3-methylbenzo-β-naphthoisospiropyran (XXV-2) (10, 11, 13).

III. CHEMICAL PROPERTIES

The spiropyrans listed in table 1 are well-crystallized substances, stable to heat, oxygen, and hydrogen. A hot solution of di-β-naphthospiropyran (XXIII-1) in chlorobenzene, when treated with a stream of oxygen for 1 hr. (6) or in toluene at 100°C. for 15 hr. (4), proved to be practically stable. Similar results were obtained with hydrogen (6).

A. Action with acids

Spiropyrans seem, in general, to react with acids to give the corresponding colored salts, e.g., when dibenzospiropyran (IV, scheme A) is treated with concentrated hydrochloric acid, one ring of the spiropyran is readily opened, yielding the colored 2-*o*-hydroxystyrylbenzopyrylium salt (II).

Dilthey and Wübken (8) showed that if the 3- and 3′-hydrogen atoms are substituted, e.g., as in 3′-methylbenzo-β-naphthospiropyran (XXII-7), there is a marked decrease in the tendency to salt formation with acids; it may become so small that, in the usual condensation with hydrochloric acid, the salt cannot be obtained at all and the spiropyran formation may be easily overlooked. For example, Decker (1) found that 3,3′-diethylspirodibenzopyran yields no salt even when its solution is saturated with hydrogen chloride gas.

Spiropyrans gave coloration with concentrated sulfuric acid ranging from orange in the case of 3,3′-dimethyl-β-dinaphthospiropyran (XXIII-8) (8) to ruby-red in the case of benzo-β-naphthospiropyran (XXII-1) (4).

Similarly, trichloroacetic acid develops the color, while acetic acid fails in the case of xantho-β-naphthospiropyran (XXIX) and benzoxanthospiropyran (XXX) (15).

B. Action with alkalies

The action of warm alcoholic potassium hydroxide on di-β-naphthospiropyran (XXIII-1) gradually gives a blood-red solution, probably owing to the formation of the potassium salt of the corresponding dinaphthylvinyl ketone (3); compare Decker (2) in the case of dibenzospiropyran (IV, scheme A). Ethyl di-β-naphthospiropyran-3,3′-dicarboxylate (XXIII-10) resists the action of boiling alcoholic potassium hydroxide (4).

C. Action with Grignard reagents

Schönberg, Mustafa, and Asker (19) have investigated the action of Grignard solutions on the thermochromic spiropyrans. The reaction of spirodi-β-naphthopyran (XI) with various Grignard reagents, e.g., phenylmagnesium bromide

TABLE 1

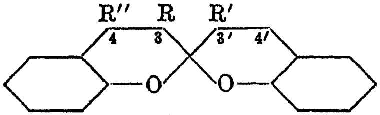
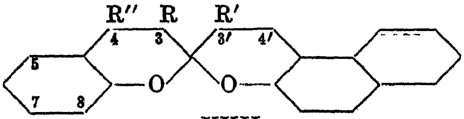
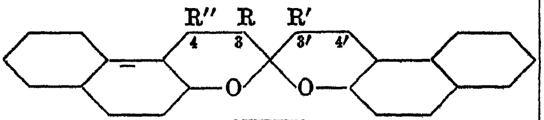
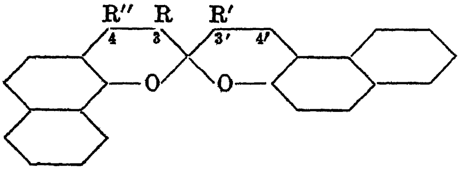
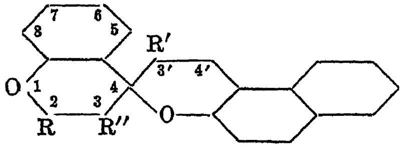
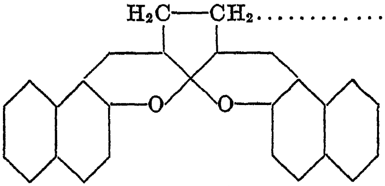
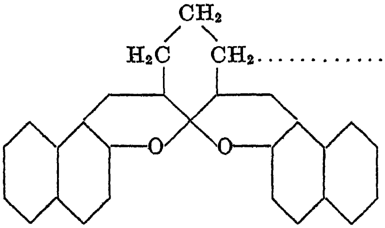
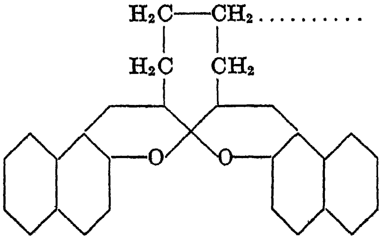
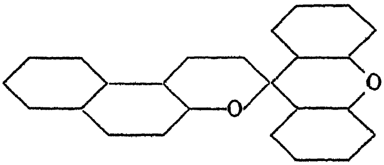
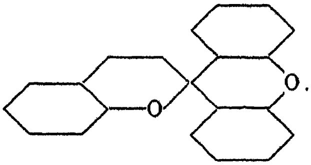
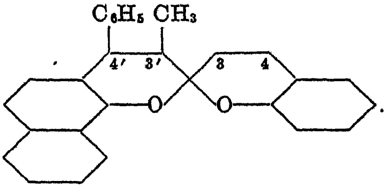
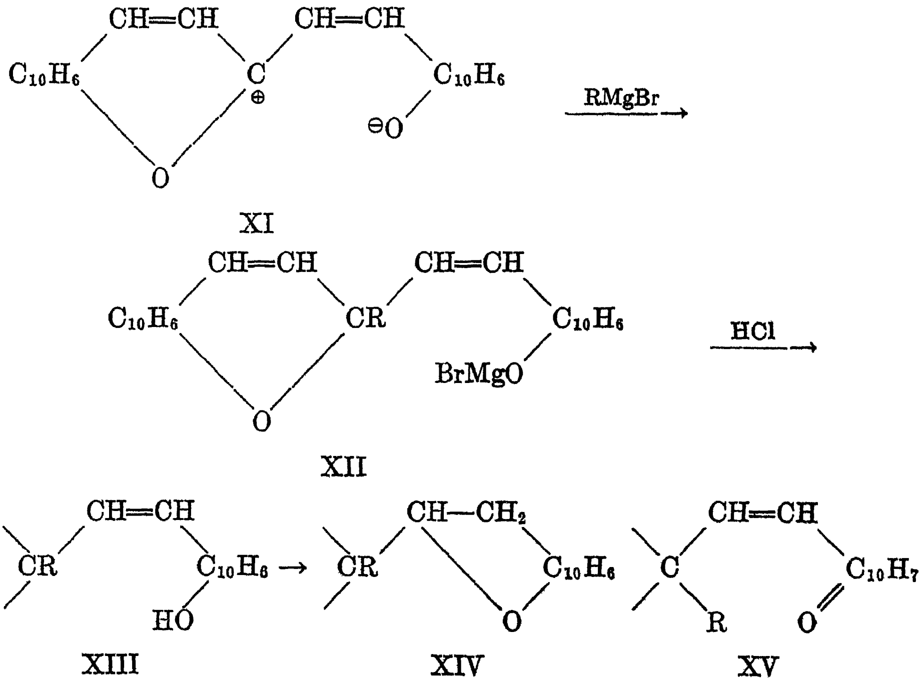
SPIROPYRAN	COLOR OF THE MELT	COLOR IN BOILING INERT SOLVENTS
 XXI		
XXI-1: $R = R' = R'' = H$	No color	Colorless
XXI-2: $R = CH_3$; $R' = R'' = H$	No color	Colorless
XXI-3: $R = C_6H_5CH_2$; $R' = R'' = H$	No color	Colorless
XXI-4: $R = R' = C_6H_5$; $R'' = H$	No color	Colorless
 XXII		
XXII-1: $R = R' = R'' = H$	Purple	Wine-red in xylene
XXII-2: $R = CH_3$; $R' = R'' = H$	Purple	Wine-red in xylene
XXII-3: $R = CH(CH_3)_2$; $R' = R'' = H$	Purple	Purple in xylene
XXII-4: $R = C_6H_5$; $R' = R'' = H$	Purple	Faint color in xylene; strong reddish blue in nitrobenzene
XXII-5: $R = CH_2C_6H_5$; $R' = R'' = H$	Purple	Reddish purple in xylene
XXII-6: $R = \beta\text{-}CH_2CH_2C_6H_5$; $R' = R'' = H$	Deep purple	Intense purple in xylene
XXII-7: $R = H$; $R' = CH_3$; $R'' = H$	No color	Colorless in xylene or veratrole
XXII-8: $R = H$; $R' = CH(CH_3)_2$; $R'' = H$	No color	Colorless in xylene or veratrole
XXII-9: $R = H$; $R' =$ octyl; $R'' = H$	No color	Colorless in diphenyl ether
XXII-10: $R = H$; $R' = CH_2C_6H_5$; $R'' = H$	No color	Colorless in xylene
XXII-11: $R = H$; $R' = \beta\text{-}CH_2CH_2C_6H_5$; $R'' = H$	No color	Colorless in xylene or veratrole
XXII-12: $R = H$; $R' = CH_3$; $R'' = C_6H_5$	No color	Colorless in xylene, veratrole, or diphenyl ether
XXII-13: $R = H$; $R' = CH_3$; $R'' = C_6H_5$, 7-OCH_3	No color	Colorless in xylene, veratrole, or diphenyl ether
 XXIII		
XXIII-1: $R = R' = R'' = H$	Tarry at 260°C.	Purple in xylene or nitrobenzene at 100°C.
XXIII-2: $R = CH_3$; $R' = R'' = H$	Not reported	Blue-violet in xylene

TABLE 1—*Continued*

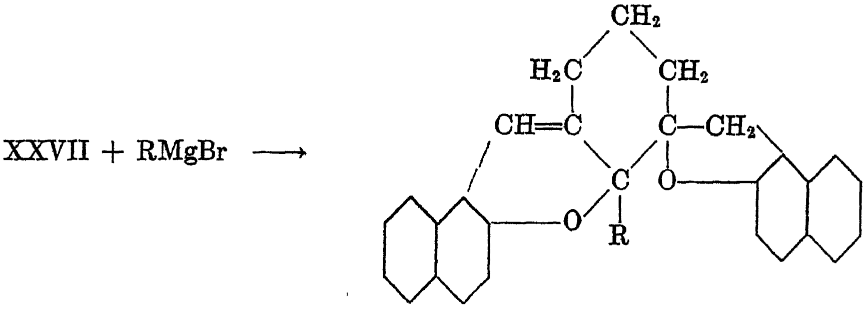
SPIROPYRAN	COLOR OF THE MELT	COLOR IN BOILING INERT SOLVENTS
XXIII-3: R = amyl; R′ = R″ = H	Not reported	Violet in pyridine
XXIII-4: R = octyl; R′ = R″ = H	Not reported	Purple in xylene
XXIII-5: R = $CH_2C_6H_5$; R′ = R″ = H	Deep blue	Blue-violet in benzene; darker in xylene
XXIII-6: R = β-$CH_2CH_2C_6H_5$; R′ = R″ = H	Not reported	Blue-purple in xylene
XXIII-7: R = C_6H_5; R′ = R″ = H	Blue	Dark violet in naphthalene
XXIII-8: R = R′ = CH_3; R″ = H	Olive-green	Colorless in xylene
XXIII-9: R = R′ = C_6H_5; R″ = H	Not reported	Colorless in inert solvents
XXIII-10: R = R′ = $COOC_2H_5$; R″ = H	Not reported	Colorless in inert solvents
 XXIV		
XXIV-1: R = H; R′ = CH_3; R″ = C_6H_5	Not reported	Colorless in xylene; pale violet in diphenyl ether
XXIV-2: R = CH_3; R′ = H; R″ = C_6H_5	Blue	The color developed is not specified
XXIV-3: R = R′ = H; R″ = C_6H_5	Deep purple	
XXIV-4: R = CH_3; R′ = CH_3; R″ = C_6H_5	Blue	Colorless in xylene; pale violet in diphenyl ether
 7 6 8 5 R′ 3′ 4′ O 1 4 2 3 O R R″ XXV		
XXV-1: R = C_6H_5; R′ = H; R″ = CH_3	Purple	Intense purple in xylene or veratrole
XXV-2: R = C_6H_5; R′ = H; R″ = CH_3, 7-OCH_3	Purple	Magenta in xylene
XXV-3; R = C_6H_5; R′ = H; R″ = C_6H_5, 7-OCH_3	Purple	Deep blue in ether containing one drop of acetic acid; pale magenta in benzene below 0°C.

SPIROPYRAN	COLOR OF THE MELT	COLOR IN BOILING INERT SOLVENTS
 XXVI	Purple	Blue color in xylene
 XXVII	Blue	Faint color in dipheny ether
 XXVIII	Not reported	Colorless in inert sol vents, even in dipheny ether
 XXIX	Deep red	Faint strawberry-pink ir veratrole; deep in diphenyl ether
 XXX	Not reported	Colorless in dipheny ether and dodecahy drosqualene
 XXXI	Not reported	Colorless in inert sol vents

followed by hydrolysis, leads to the formation of 2,3-dihydrofuran derivatives (XIV) and not of phenolic compounds (XIII). XIV (R = C_6H_5) is insoluble in aqueous alkali solution; it is not attacked by ethereal diazomethane solution or by benzoyl chloride in the presence of pyridine, and is stable towards methyl sulfate in the presence of alkali. These properties make it improbable that the reaction product has the character of an enol or of a potential enol (XIII or XV). The diene reaction of XIV with maleic anhydride is negative. The reaction proceeds according to the following scheme:



Similarly, the action of Grignard reagents on 3,3′-trimethylenespirodi-β-naphthopyran (XXVII) leads to products which show properties analogous to those of XIV (R = C_6H_5). These compounds are therefore formulated as XVI.

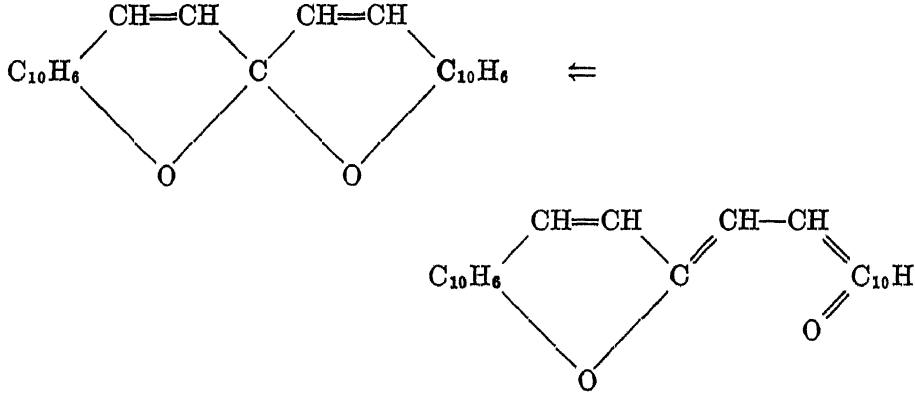


XVI

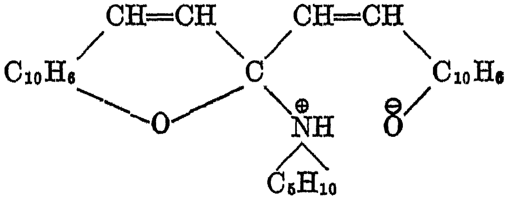
IV. COLOR PHENOMENA ASSOCIATED WITH SPIROPYRANS

The substances mentioned in table 1 are, in general, colorless crystalline compounds; some of them exhibit the property of forming, in cold inert solvents, colorless solutions which develop an intense violet-blue color on heating; on cooling, the color disappears and the substance is recovered almost unchanged. This phenomenon has been studied chiefly by Heilbron, Löwenbein, Dilthey, and their respective schools.

One view which has been advanced by Löwenbein and Katz (16) accounts for this phenomenon by intramolecular change from the spiro type to the *o*-quinoid system, as illustrated below:

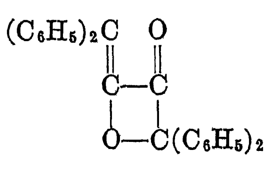


Dilthey and coworkers (6, 7) reject the quinoid hypothesis on the grounds that, whereas true quinones mostly show a bathochromic effect in piperidine solution and never a hypsochromic action, di-β-naphthospiropyran (XXIII-1) gives a yellow solution which is unaffected by heat (7). The disappearance of color in the salts formed by the interaction of the spiropyran and piperidine shows that the chromophore, the positively charged carbon atom, is absent (XVII).

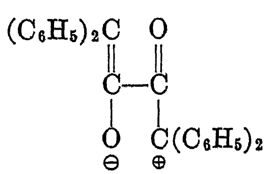


XVII

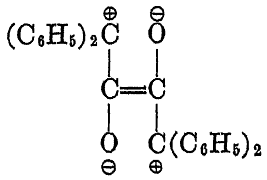
Salts of this type have so far not been isolated, but the correctness of Dilthey's conception is greatly strengthened by the observation of Schönberg and Sina (20) that the dimeric permanganate-colored diphenylketene (XVIII), which has the constitution of a betaine (XIXa or XIXb), dissolves in cold piperidine yielding an almost colorless solution, from which the colorless piperidinium salt (XX) may be obtained. When the salt is heated, piperidine is split off and the dimeric diphenylketene is regenerated (compare scheme F).



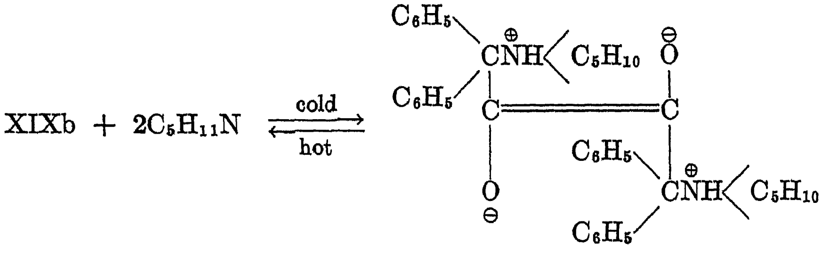
XVIII



XIXa



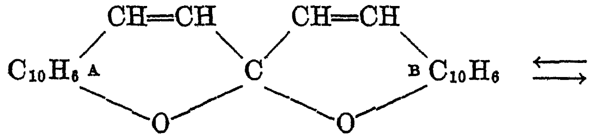
XIXb



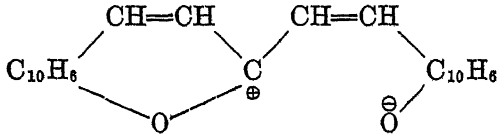
XX

(F)

Dilthey and coworkers (6, 7) conclude that the appearance of color is due to ionic dissociation, the colored form being represented as a heteropolar molecule, as illustrated below.



(colorless in the cold)



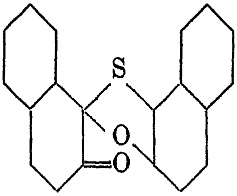
(G)

(violet-blue on heating)

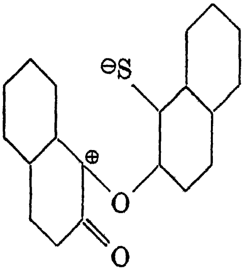
The possibility of the phenomenon being due to free-radical formation has been excluded by Dilthey (6, 7) and Löwenbein (16); both showed that the molecular weights of these compounds are normal, whether the solution is colored or not. Dickinson and Heilbron (4) found that the color is unchanged by the addition of quinol, a reagent which almost instantaneously reduces all the known types of radicals, with disappearance of the color.

Recently, Schönberg, Mustafa, and Asker (19) have shown that a possible approach to this color phenomenon may be to apply the theories used to explain the stability of the free radicals of the triphenylmethyl type. It has been pointed out (compare Gilman, *Organic Chemistry*, 2nd edition, page 1979) that the free radicals formed by the dissociation of hexaphenylethane are stabilized by resonance, and it seems possible that this theory may also explain the stability of the zwitter ions such as XI. On the other hand, the lowered stability of the spirans may be due to their non-polar configuration (see rings A and B in scheme G) interfering with the development of resonance.

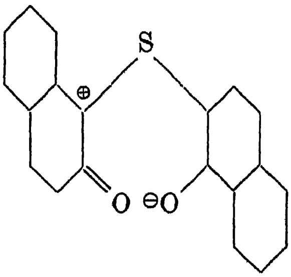
All the spiropyrans so far investigated show the betaine structure (compare scheme G) (18, 19, 20) only in solution and the question arises whether colored spiropyrans may be found which owe their color, even in the solid state, to the presence of a positively charged carbon atom. This seems to be the case. It has been found (17) that dehydro-β-naphthol sulfide (21) probably belongs to this group of substances. Structure XXXII does not explain the deep red color of the substance and it is believed that it must be regarded as an enol or thio-enol betaine (XXXIIIa or XXXIIIb).



XXXII

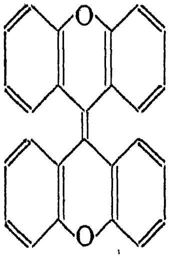


XXXIIIa

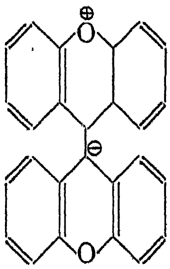


XXXIIIb

The thermochromic behavior of the spiropyrans may be related to that of certain ethylenes, e.g., XXXIVa and XXXIVb (18). This phenomenon has also been explained by the formation of betaines, as illustrated below:



XXXIVa
(colorless in the cold)



XXXIVb
(bluish-green on heating)

Dickinson and Heilbron (4) showed that the determining factors for the color development in spiropyrans are: (*a*) that at least one naphthalene ring be present and (*b*) that the 3′-carbon atom in the naphthopyran ring be unsubstituted. The color phenomenon is the result of a series of changes in which equilibrium is established between the neutral spiropyran and an ionized compound (compare scheme G).

Later, Dilthey and Wübken (8) drew a parallel between the ease with which spiropyrans undergo salt formation in the presence of acids (forming styrylpyrylium salts) and the ease with which they change color on heating in inert solvents: they regarded the two changes as analogous. Their arguments are based on the behavior of 3,3′-trimethylene-β-naphthospiropyran (XXVII), which develops a distinct color in boiling diphenyl ether and dissolves in acetic acid without color, i.e., no salt formation, but in trichloroacetic acid gives a violet color. Further investigations by Dickinson and Heilbron and coworkers (5) showed that while 3′-methylbenzo-β-naphthospiropyran (XXII-7) undergoes no color change in diphenyl ether, 3-methylbenzo-β-naphthospiropyran (XXII-2) develops the usual wine-red color; both dissolve in acetic acid yielding colored solutions due to salt formation. On the basis of Dilthey and Wübken's view (8), both substances would be expected to develop color in diphenyl ether. Their failure to do so shows that the ease of formation of the ionic anhydro base is not strictly comparable to salt formation.

According to the experimental facts, Heilbron and coworkers (4, 5, 9, 14) came to the following conclusions: (*a*) Dibenzospiropyrans (XXI-1) do not develop any color change on heating in inert solvents. (*b*) Benzo-β-naphthospiropyrans (XXII-1) containing a substituent in the 3′-position fail to give a color change. (*c*) Di-β-naphthospiropyrans (XXIII-1) containing a substituent in both the 3- and 3′-positions fail to give colored solutions. (*d*) Spiropyrans having a phenyl group at position 4 (in the benzo-β-naphthospiropyran molecule) (XXII) behave normally in developing the color change, except for 4-phenyl-3′-methylbenzo-β-naphthospiropyran (XXII-12) and its 7-methoxy derivative (XXII-13) which give a coloration on heating in xylene solution, although substituted in the 3′-position (11). (*e*) α,β-Dinaphthospiropyrans appeared to differ from those encountered in the di-β-naphthospiropyran series, since a coloration is developed even with substituents in both the 3- and 3′-positions, e.g., 4-phenyl-3,3′-dimethyl-α,β-dinaphthospiropyran (XXIV-4) (11, 12). (*f*) Benzo-α-naphthospiropyrans, e.g., 4′-phenyl-3′-methylbenzo-α-naphthospiropyran (XXXI), behaved normally in failing to give a colored solution in inert solvents of high boiling points. (*g*) Substituted benzo-β-naphthoisospiropyrans (XXV), e.g., 2-phenyl-3-methylbenzo-β-naphthoisospiropyran (XXV-1), where the 3′-position is unsubstituted, develop colored solutions as normal spiropyrans do (10, 12, 13).

V. REFERENCES

(1) Decker, H., and Fellenberg, T. von: Ann. **364**, 1 (1909).
(2) Decker, H., and Felser, H.: Ber. **41**, 2997 (1908).
(3) Dickinson, R., and Heilbron, I. M.: J. Chem. Soc. **1927**, 14.
(4) Dickinson, R., and Heilbron, I. M.: J. Chem. Soc. **1927**, 1699.
(5) Dickinson, R., Heilbron, I. M., and O'Brien, F.: J. Chem. Soc. **1928**, 2077.
(6) Dilthey, W., Berres, C., Hölterhoff, E., and Wübken, H.: J. prakt. Chem. **114**, 179 (1926).
(7) Dilthey, W., and Wizinger, R.: Ber. **59**, 1856 (1926).
(8) Dilthey, W., and Wübken, H.: Ber. **61**, 963 (1928).
(9) Heilbron, I. M., Heslop, R. N., Irving, F., and Wilson, J. S.: J. Chem. Soc. **1931**, 1336.

(10) HEILBRON, I. M., HESLOP, R. N., AND HOWARD, G. F.: J. Chem. Soc. **1933**, 1263.
(11) HEILBRON, I. M., HESLOP, R. N., AND IRVING, F.: J. Chem. Soc. **1933**, 430.
(12) HEILBRON, I. M., HEY, D. H., AND LOWE, A.: J. Chem. Soc. **1936**, 1380.
(13) HEILBRON, I. M., AND HOWARD, G. F.: J. Chem. Soc. **1934**, 1571.
(14) HEILBRON, I. M., AND IRVING, F.: J. Chem. Soc. **1929**, 936.
(15) IRVING, F.: J. Chem. Soc. **1929**, 1093.
(16) LÖWENBEIN, A., AND KATZ, W.: Ber. **59**, 1377 (1926).
(17) SCHÖNBERG, A.: Private communication.
(18) SCHÖNBERG, A., AND ASKER, W.: Chem. Revs. **37**, (1945); SCHÖNBERG, A., ISMAIL, A. F., AND ASKER, W.: J. Chem. Soc. **1946**, 442.
(19) SCHÖNBERG, A., MUSTAFA, A., AND ASKER, W.: J. Chem. Soc. **1947**, 847.
(20) SCHÖNBERG, A., AND SINA, A. T.: J. Chem. Soc. **1947**, 175.
(21) WARREN, L. A., AND SMILES, S.: J. Chem. Soc. **1930**, 958.

RECENT DEVELOPMENTS IN THE STUDY OF HYDROGEN OVERPOTENTIAL

J. O'M. BOCKRIS

Department of Chemistry, Imperial College of Science, London, S.W. 7, England

Received March 19, 1948

The present position of hydrogen overpotential studies is discussed. Owing to the large discrepancies still apparent among recent experimental determinations of overpotential, an outline of modern experimental technique and a critical survey of evidence regarding the effect of the different variables on hydrogen overpotential are given. The various suggested theories are described and critically compared with the experimental data.

CONTENTS

I. Introduction 526
II. The technique of measurements of hydrogen overpotential 527
  A. Electrolytic cell and its use 527
  B. Preparation of electrodes 529
  C. Preparation of the solution 530
  D. Methods of measurement of overpotential 530
  E. Technique of establishment of the overpotential–log current density relation (or "Tafel line") 532
III. The experimental facts of hydrogen overpotential 533
  A. Discrepancies between the results of different workers 533
  B. Electrode factors 533
    1. Effect of current density 533
      (a) Mercury at low current densities 534
      (b) Mercury at high current densities 535
      (c) Cathodes other than mercury at low current densities 535
      (d) Cathodes other than mercury at high current densities 536
      (e) Experimental evidence on the *b* factor 537
    2. Effect of temperature 537
    3. Effect of change of state 538
    4. Effect of pressure 538
    5. Effect of time 539
      (a) Build-up 539
      (b) Decay 539
    6. Effect of electrode material 540
    7. Effect of surface properties 540
    8. Effect of diffusion through the cathode 541
    9. Effect of shape and curvature of cathode 543
    10. Effect of alloy formation 543
  C. Solution factors 543
    11. Effect of hydrogen-ion concentration 543
    12. Effect of foreign salts 544
    13. Effect of solvent 544
    14. Effect of catalytic poisons and activators 546
    15. Effect of gaseous depolarizers, e.g., oxygen 547
    16. Effect of colloids 547
    17. Effect of radiation 548

IV. The theory of hydrogen overpotential........ 548
  A. General equations at a working hydrogen electrode........ 548
    1. Definition of currents at cathode and anode........ 548
    2. The Tafel equation........ 548
    3. The reaction $2H^+ + 2e \rightarrow H_2$ at the working hydrogen electrode: principal theories of hydrogen overpotential........ 549
  B. The slow discharge theories........ 552
    1. General slow discharge theory........ 552
      (a) Essential theory........ 552
      (b) Development of the general theory of slow discharge........ 553
      (c) Fundamental aspects of the general slow discharge theory........ 554
    2. The (energy level) slow discharge theory........ 555
    3. Hydrogen molecule ion theory........ 557
    4. Slow prototropic transfer theory........ 558
      (a) Essential theory........ 558
      (b) Fundamental aspects of the slow prototropic transfer theory........ 560
  C. Slow combination theories........ 562
    1. Catalytic theory........ 562
      (a) Quasi-thermodynamic catalytic theory........ 562
        (i) Essential theory........ 562
        (ii) Fundamental aspects of the quasi-thermodynamic catalytic theory 564
      (b) Kinetic catalytic theory........ 564
    2. Electrochemical theory........ 566
  D. Miscellaneous theories........ 568
  E. Discussion........ 568
    1. Quantities relevant to hydrogen overpotential and open to quantitative determination........ 568
      (a) α and the exchange current........ 568
      (b) λ, the net charge........ 568
      (c) Limiting current density........ 568
      (d) Temperature coefficient and energy of activation........ 568
      (e) pH and salt effects........ 569
      (f) Decay........ 569
      (g) Solvent effect........ 569
      (h) Rate of single stages of the reaction at working hydrogen electrodes. 569
      (i) Capacity of the electrode–solution interface........ 569
    2. Matters of contemporary interest in the interpretation of experimental results........ 570
      (a) Current density........ 570
      (b) Temperature........ 571
      (c) pH and salt effects........ 571
      (d) Time........ 571
      (e) Surface........ 572
      (f) Transfer by diffusion........ 572
      (g) Experimental criteria for the elucidation of the fundamental reaction mechanisms at a working hydrogen electrode........ 574
V. Summarizing remarks........ 574
VI. References........ 574

I. INTRODUCTION

The recent work of Frumkin (67, 71, 72) and his collaborators, of Eyring, Glasstone, and Laidler (57), and of Hickling (90, 95) has served to redirect attention to the unsolved problems of hydrogen overpotential and to emphasize that considerable differences still exist between the theoretical views of modern authors. This is due primarily to the unexpected complexity of the phenomena and to the fact that only in recent years has experimental work been carried out which is relatively free from vitiating factors.

A full-length review (162) has not been devoted solely to this subject for many years, and the following is intended as a critical survey of the present state of the experimental and theoretical fields.

Hydrogen overpotential at a given current density of *i* amp./sq. cm. is defined as the difference between the potential of an electrode at which hydrogen is being evolved at *i* amp./sq. cm. and the potential of the reversible hydrogen electrode in the same solution. This potential difference may consist of three contributions: (*1*) that due to the ohmic potential difference between the electrode and the Luggin capillary (see below); (*2*) that due to concentration changes in the diffusion layer near the electrode surface; and (*3*) that associated with the activation energy of some stage of the reaction

$$2BH^+ + 2e \rightleftharpoons H_2(\text{gas})$$

(where B represents the solvation sheath round the proton). Hydrogen activation overpotential (31) is the specific term applied to the latter type of overpotential. In the following, hydrogen overpotential will generally be taken as synonymous with hydrogen activation overpotential on the assumption that, in the experimental arrangement, the two other contributions to the potential difference between working and stationary electrodes have been reduced to negligible proportions.

In the following, overpotential will be given its absolute sign, e.g., the hydrogen overpotential at a mercury cathode in dilute aqueous acid solution, at a current density of 10^{-3} amp./sq. cm., is about -1.04 v. Increase or decrease of overpotential means that the cathode potential becomes, respectively, more negative or less negative with respect to the reversible hydrogen electrode in the same solution.

II. THE TECHNIQUE OF MEASUREMENTS OF HYDROGEN OVERPOTENTIAL

A. ELECTROLYTIC CELL AND ITS USE

Typical designs of modern cells are shown in figures 1 (22) and 2 (107).

The essential requirements of a cell are that it should (*i*) maintain a hydrogen atmosphere against atmospheric oxygen, (*ii*) maintain catholyte separate from the anolyte and from the hydrogen electrode, and (*iii*) be provided with a suitable, preferably adjustable, "cathode tip" or Luggin capillary (125) to connect the cathode to the reference electrode. It is undesirable to grease taps and joints (123) which should be wetted with the solution and sealed to the outer atmosphere by solution-filled traps, able to withstand a vacuum (see figures 1 and 2). Outside the current density range of 10^{-8} to 10^{-2} amp./sq. cm. more specialized provisions (19, 32, 110) are necessary. Above the current density of 10^{-3} amp./sq. cm. it is not necessary to guard the solution from every trace of oxygen (19, 92).

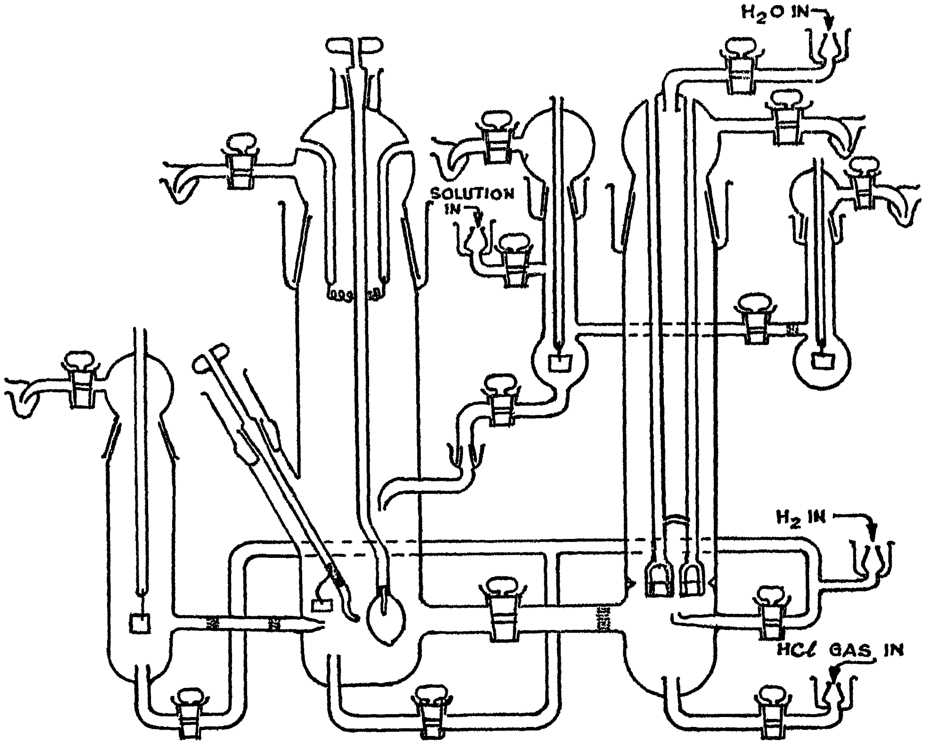


FIG. 1. Electrolytic cell for measurement of hydrogen overpotential

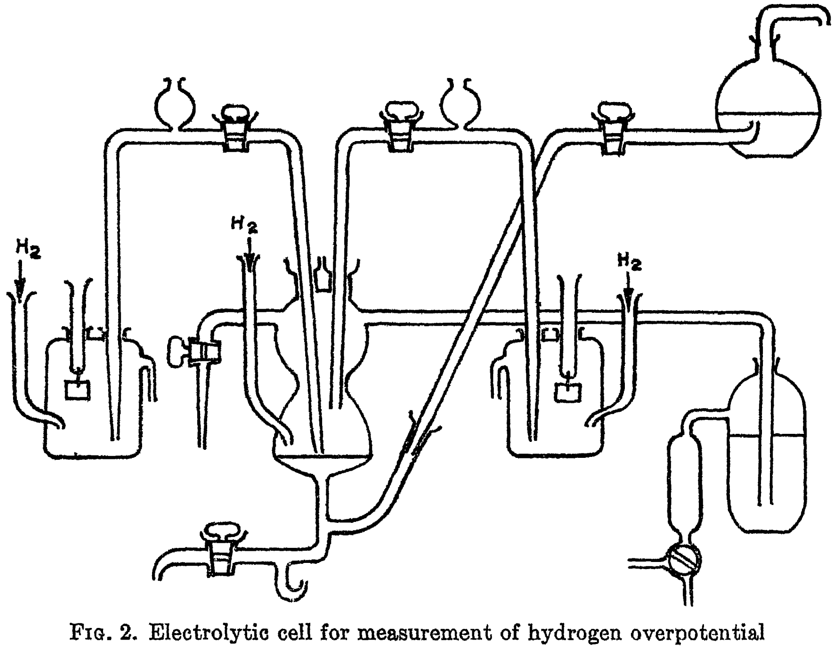


FIG. 2. Electrolytic cell for measurement of hydrogen overpotential

Cells, preferably cleaned with nitric–sulfuric acid mixture, should be washed with distilled water and then conductivity water for many hours before use. Drying agents for use with non-aqueous solvents, e.g., acetone, should be distilled before use to avoid the deposition of solid matter upon evaporation.

B. PREPARATION OF ELECTRODES

Mercury of appropriate purity can be obtained fairly easily by the double or triple distillation of mercury, first purified electrolytically by von Naray-Szabo's method (159).

Solid electrodes are difficult to prepare in a clean and reproducible state, and the many types of pretreatment described contribute considerably to the lack of agreement between the results of many authors. Chemical pretreatment is unsatisfactory, because products of the cleaning reaction may become occluded in the metal surface. It has been stated that relatively reproducible results can be obtained simply by washing with water and wiping the cathode surface with a filter paper (19); for soft metals scraping with a sharp knife can be employed (82, 106) if precautions (13) are taken (e.g., microscopic examination) to observe that no particles from the knife remain in the electrode.

Most former methods of preparation of solid electrodes have the disadvantage that they allow exposure of the cleaned surface to the atmosphere before immersion in the hydrogen-filled cell. Grease (1) and an oxide film may collect on the electrode in a few seconds and obscure the significance of, for example, the slow growth of overpotential with time.

Some kind of standard state of the electrode surface is clearly desirable and an attempt has been made to obtain this (Bockris and Conway (21)) by sealing the wire cathode in a stream of pure hydrogen (after prolonged preheating) into a narrow glass tube ending in a thin glass bulb. The cathode, thus annealed and preserved in a hydrogen atmosphere, is then introduced into the cell which is later filled with hydrogen and solution, after which the glass bulb (enclosing the hydrogen atmosphere round the electrode) is broken under the hydrogen-saturated solution (see figure 1). The method probably eliminates oxide films[1] and grease on the surface and avoids the difficulties involved in the attachment of solid electrodes to glass by cements. Effects of adhesives in solution have been stressed in work on electrode capacities (74) but insufficiently in work on overpotential. Bockris and Parsons (24) observed that not only organic but also many types of inorganic cements, though dissolving in aqueous acid solutions to the extent of only 10^{-6} gram-moles/liter in 12 hr., had an appreciable effect on overpotential at a current density of 10^{-3} amp./sq. cm. at platinized platinum electrodes.

The shape of the cathode is important because of the desirability of a uniform distribution of current density over all its parts. A plate is better in this respect than a wire, for which in most cell configurations the current lines tend to concentrate at the end nearest to the anode (79).

---

[1] Complete elimination thus of oxide films may be negated by the reaction $M + H_2O \rightarrow MO + H_2$, which possibly occurs for a very brief time after the electrode M contacts

C. PREPARATION OF THE SOLUTION

The apparatus should be of glass throughout, because no contact between the vapor of the solution and rubber bungs is desirable. The solvent used is distilled in hydrogen after other methods of preparation have been carried out. An appropriate criterion of the purity of the solvent is its electrical conductivity, which should be $< 10^{-6}$ mhos/cm. cube. The solution is preferably produced by dissolving a gaseous solute in the solvent. The solid source of the solute, e.g., potassium chloride of analytical reagent purity, should be heated to some 50°C. below its melting point in a hydrogen atmosphere for several hours to remove organic impurities present (107). The concentration of the gaseous solute is conveniently determined conductimetrically for both aqueous and non-aqueous solutions (25), the electrodes being in the vessel into which pass the solute gas and a vigorous stream of hydrogen for stirring purposes.

Non-gaseous solutes invariably contain appreciable quantities of heavy metal impurities and are therefore better avoided. Their use necessitates very thorough purification by repeated distillation and electrolysis.

After initial purification the solution still contains impurities, which are most efficiently removed by cathodic polarization (i.e., deposition, reduction, adsorption) on a cathode of the same material as the working cathode (72, 124). Cathodic "prepolarization" is continued on an auxiliary electrode of the material of the cathode under examination for many hours, often at fairly low current density. The exact conditions for satisfactory purification of a given solution with a given cathode material can only be finally established by experiment, the criteria of efficient purification being (*i*) reproducibility of results, and (*ii*) no further change in overpotential caused by further increase in the quantity of current passed through the solution (25). Few workers have used these more stringent methods for the preparation of solutions. In particular among modern workers, Hickling (90) does not consider the purification outlined above necessary for work at higher current densities. This may be relatively true with respect to depolarizers such as oxygen, but other active impurities in small traces may cause alteration in the slope of the overpotential–log current density line as well as in the actual values of the hydrogen overpotential (see figure 3) (123). Even at 10^{-1} amp./sq. cm., the overpotential on copper electrodes is some 5 cv.'s higher in prepolarized than in non-prepolarized solutions (19).

The method of preparation of alkaline solutions is less certain. Lukovtsev, Levina, and Frumkin (127) use sodium amalgam. It seems that this method may lead to the presence of mercury in solution unless cathodic prepolarization is carried out for a very considerable time.

The hydrogen used is preferably produced electrolytically. It may contain appreciable quantities of oxygen, hydrogen sulfide, carbon monoxide, and carbon dioxide and should be passed through appropriate absorbing agents (preferably not liquids) (24) and several liquid-nitrogen traps (124) before entry to the cell.

D. METHODS OF MEASUREMENT OF OVERPOTENTIAL

The so-called "direct method" consists in a direct comparison of the potential of the working electrode with that of some standard reversible electrode, in the same solution as the former, by means of a potentiometer. Inclusion of an ohmic potential difference in the measured potential difference between working and stationary electrodes is avoided by pressing the Luggin capillary (diameter approximately 1 mm.) firmly against the cathode. This simple method suffers from several disadvantages: (*i*) part of the electrode surface is shielded from its share of the current lines; (*ii*) at high current densities the potential difference between the end of the tip and the electrode becomes significant. According to some (76, 81, 131) there is a gas film between electrode and solution at all current densities and the relatively high resistivity of this causes an appreciable ohmic overpotential to exist even at, say, 10^{-3} amp./sq. cm. This concept has been convincingly disproved (44, 59, 61). The presence of an oxide film on the cathode surface may, however, lead to the setting up of a considerable ohmic overpotential similar to that which would be caused by a transfer resistance. In normal aqueous acid solutions, the direct method of measurement can be used up to a current strength of about 10^{-1} amp./sq. cm. and at higher current densities with the special precautions mentioned below.

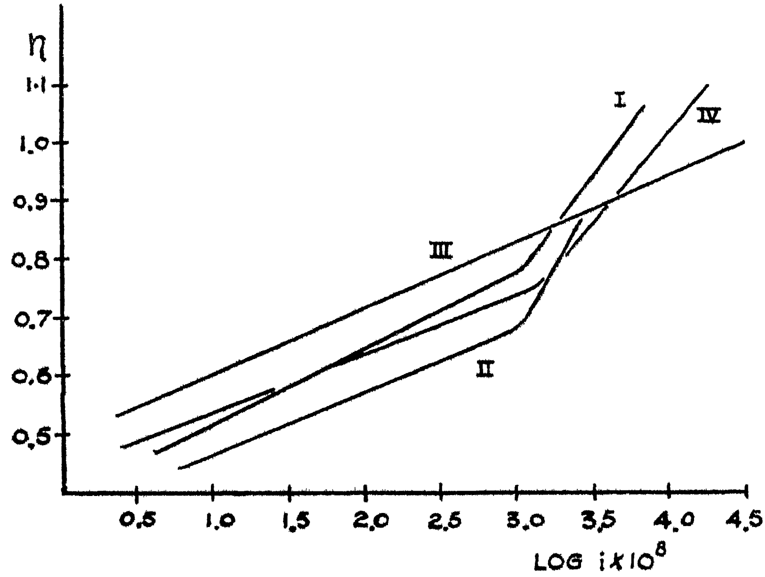


FIG. 3. Plot of hydrogen overpotential *versus* log current density. Curves I and II (II joins III) show the effect of grease on the taps of the electrolytic cell; curve IV shows the effect of other poisons. Curve III is from work in carefully purified solutions.

The indirect or commutator method of measurement (131) involves the intermittent passage of current across the electrode–solution interface, measurements of potential being made in the periods when the current is not flowing, a procedure which thus eliminates ohmic overpotential. A disadvantage attaching to this method is that intermittent electrolysis may produce different conditions at the electrode surface compared to those occurring with continuous electrolysis. Further, the rapid decay of overpotential with time (5) makes it necessary to measure the former very quickly and at a rapid succession of intervals, after the cessation of the polarizing current, so that extrapolation to zero time can be accurately made. Incorrect extrapolation consequent upon a too long interval before the first reading is recorded caused error in the earlier commutator method (76, 115, 143). More recently Hickling (88) has used an electronic interrupter, the essence of which is a thyratron valve in which the period of interruption is of the order of 5×10^{-5} sec. and which thus considerably facilitates a correct extrapolation. According to Frumkin (71), this commutator is also open to the criticism of incorrect extrapolation at current densities greater than 10^{-3} amp./sq. cm., owing to the extreme rapidity of the first stage of the exponential decay. Bockris (13), however, using the direct method of measurement and the same type of solution preparation as that used by Hickling and Salt (90), found agreement with results obtained using Hickling's commutator interrupter up to a current density of 10^{-1} amp./sq. cm., so that, because possible electrical errors from each method are of opposite sign, the validity of Hickling's commutator method seems confirmed up to this current density.

At very high current densities the rapid decay of overpotential causes the extrapolation from all modifications of the commutator method to be inaccurate, so that the direct method must be applied with the following precautions (19, 110): (*i*) A very small cathode area is used, thus reducing the ohmic overpotential (which depends on current *strength*) and also heating effects in the solution; (*ii*) very rapid rate of streaming of the electrolyte to reduce concentration polarization to negligible proportions; (*iii*) a configuration of the cathode, preferably a very short thin wire, which allows accurate calculation of the resistance between cathode tip and cathode. Some authors (90) consider this calculation to be inherently inaccurate, owing to the existence of an unknown specific conductivity in the diffusion layer; others (71) consider it permissible to use the bulk specific resistance. The latter view seems incorrect and the problem of an appropriate correction formula is very difficult because of the lack of information concerning the exact hydrodynamical conditions during rapid streaming.

Ferguson and Bandes (60) have recently reported a device for the convenient photographic recording of the variations of overpotential with time and rate of polarization, and this has been applied to the study of decay and of ohmic overpotential.

E. TECHNIQUE OF ESTABLISHMENT OF THE OVERPOTENTIAL–LOG CURRENT DENSITY RELATION (OR "TAFEL LINE")

The marked variation of the hydrogen overpotential on some metals with time (13, 90) makes it necessary to choose a time of polarization after which the potential difference between the working and stationary electrodes should be termed the overpotential. Workers who consider the time variation to be due to the electrodeposition of impurities, or to other secondary phenomena, have generally made measurements shortly after the commencement of polarization at a given current density. Some authors (116) state 1 min. to be this time. This procedure is satisfactory on metals for which the variation of overpotential with time is relatively small. For some metals, however, it is considerable, so that this method of "quick runs" may vitiate a comparison of results obtained at various current densities.

The fact that intensive purification of the solution and prepolarization do not completely eliminate the variation of overpotential with time on mercury cathodes (71) and that it appears to be a function of the mode of preparation of the electrode surface, has led some workers (13, 90) to the view that this property is a primary characteristic of overpotential, in which case it appears to be more reasonable to take the overpotential after it has reached the steady state, i.e., after electrolysis lasting from a few minutes to several hours ("slow runs"). It has been claimed (90) that this method provides a standard condition under which all metals can be examined; its validity rests upon the unproved view that the variations with time are not due to true impurities.

A further discrepancy in technique is between authors who start polarization from the moment the electrode contacts the solution to the end of the experiment and those who cease polarization between each current density and allow the cathode potential to reach a "static potential" before polarizing at another current density. The latter method minimizes the possibility that polarization set up at one current density may affect the steady state set up at the next (90). Conversely, dissolution of the metal may take place during the resting periods between the various current densities.

III. The Experimental Facts of Hydrogen Overpotential

A. DISCREPANCIES BETWEEN THE RESULTS OF DIFFERENT WORKERS

Difficulties met in comparison of results of different workers are connected firstly with lack of rigor in purification of the solution, with a lack of comparability in the preparation of the electrode surface, and with factors connected with the time variations of overpotential. Thus, the large amount of work carried out by Frumkin and his coworkers has not been clarified by the earlier absence in their work of an attempt to deal with the problem of variation with time, which has more recently been admitted by them both for metals of low overpotential, e.g., nickel (120, 127) and palladium (73), and for mercury (71). In the following an attempt has been made to collect evidence from sources in which sufficient experimental detail is given to assess the reliability of the results.

Experimental results have been regarded as being concerned either with "electrode factors", e.g., time, or "solution factors," e.g., pH.

B. ELECTRODE FACTORS

1. Effect of current density

According to Tafel (153), over certain current density ranges and for certain electrodes, the relation between overpotential (η) and current density (i) is

$$\eta = a - b \log i$$

or

$$i = e^{(a-\eta)/b}$$

where a and b are constants (Tafel equation).

(a) Mercury at low current densities

The older results of Bowden and Rideal at 15°C. (35) are some 5 cv. lower in 0.2 N sulfuric acid than those of Jofa (102) in 0.1 N sulfuric acid over the range 10^{-6} to 10^{-3} amp./sq. cm. These latter data at 20°C. over the current density range 10^{-7} to 3×10^{-2} amp./sq. cm. are given by:

$$\eta = -1.426 - 0.113 \log_{10} i$$

Jofa (102) also measured overpotential in 0.1 N aqueous hydrochloric acid solution: If correction is made for differences in temperature of measurement, they agree to within about 9 mv. with those of Levina and Sarinsky (123). Below 10^{-7} amp./sq. cm. difficulties of measurement increase markedly because (*i*) the region of the electrocapillary maximum is approached, so that the probability of adsorption of surface-active impurities is increased; (*ii*) the effect of traces of depolarizers is more marked; (*iii*) at current densities as low as 10^{-10} amp./sq. cm. the double layer takes an appreciable time to charge up. Bowden and Grew (32) tried to overcome difficulties (*i*) and (*ii*) by enclosing the cathode in glass and succeeded in confirming the linearity of the overpotential–log current density relation down to about 10^{-9} amp./sq. cm. Some deviations at lower current densities were observed, the cathode potential being more negative than that expected from the Tafel equation. If i of Tafel's equation $= i_0$ for $\eta = 0$, values of i_0 obtained in aqueous acid solutions at about 20°C. are as shown in table 1. Comparable results on mercury at low current densities are thus in good agreement.

TABLE 1

Values of i_0 obtained in aqueous acid solutions

WORKER	i_0 *amp./sq. cm.*	SOLUTION
Bowden and Rideal (35)	3×10^{-12}	0.5 N H_2SO_4
Bowden and Kenyon (113).	6×10^{-12}	0.2 N H_2SO_4
Jofa (102).	5×10^{-13}	0.1 N H_2SO_4
Jofa and Mikulin (108).	1.5×10^{-12}	0.25 N H_2SO_4
Jofa (107).	1.8×10^{-12}	0.1 N HCl
Bockris and Parsons (24).	5.2×10^{-13}	0.1 N HCl
Bockris and Parsons (24).	1.3×10^{-12}	1.0 N H_2SO_4

Mituya (129) has also carried out experiments in the current density range 1.87×10^{-9} to 4.3×10^{-11} amp./sq. cm. In the rectilinear part of the Tafel line the observed value of b was 0.186 at 0°C. in 0.1 N hydrochloric acid, and the values of the overpotential are about 0.2 v. lower than those expected from other work. Insufficient precautions seem to have been taken by this worker for prevention of the diffusion of platinum from the anode, which may have reached the cathode in his experiments, a fact which is probably the basis of the discrepancies in *a* and *b* of the Tafel equation between this and other work cited above.

(b) Mercury at high current densities ($> 10^{-3}$ amp./sq. cm.)

Work at high current densities is difficult for the following reasons: (*i*) ohmic overpotential tends to become marked, especially in dilute solution; (*ii*) the limiting current density may be approached in the absence of efficient aids to diffusion; (*iii*) excessive heating of the solution may occur; (*iv*) liquid mercury undergoes an oscillatory motion; this makes it preferable to use amalgamated copper electrodes upon which the overpotential is less than 10 mv. different from that on pure mercury at current densities greater than 10^{-4} amp./sq. cm. (19). The effect of (*iii*) can be minimized by using electrodes of small electrodes areas (19, 110). The influence of concentration overpotential is more difficult to assess, owing to the uncertain values of the thickness of the diffusion layer in agitated solutions.

Frumkin (71) maintains that no limiting current density due to concentration overpotential occurs even at a current strength of 1 amp. in a well-agitated solution. Kabanov (110) used rapid shearing of the electrolyte, Hickling and Salt (90) agitation by passage of a rapid gas stream, and Dolin (45) mechanical stirring to minimize the contributions of concentration polarization. Resistance overpotential corrections were calculated by Kabanov (110), who measured the distance between cathode and electrode tip with a microscope and assumed that the appropriate specific resistance was that of the bulk of the solution, a procedure of doubtful validity. Corrections in Kabanov's work were of the same order as the measured overpotential at the highest current densities. Hickling and Salt (90) made use of an electronic commutator up to a current density of 10 amp./sq. cm.

Fairly large discrepancies exist between the results of Kabanov, which may be represented by the equation:

$$\eta = -1.42 - 0.14 \log_{10} i$$

and those of Jofa, for which the corresponding equation is:

$$\eta = -1.396 - 0.116 \log_{10} i$$

Kabanov's results on amalgamated mercury indicate that the Tafel equation is applicable on this metal up to a current density of 10 amp./sq. cm. (The points on the Tafel line show a scatter of 0.04 among themselves.) Conversely, Hickling and Salt (90) found that at current densities greater than 10^{-2} amp./sq. cm. the Tafel equation could no longer be used to express the results, a fact which indicated that the cathode potential was less negative (i.e., overpotential lower) than would have been so according to a linear Tafel line.

(c) Cathodes other than mercury at low current densities

According to Bowden and Rideal (35), the Tafel equation is applicable to the variation of hydrogen overpotential on silver, nickel, platinum, and carbon over the current density range 10^{-7} to 10^{-3} amp./sq. cm., the *b* value for these metals being about 0.10–0.12 for the first three and 0.84 for carbon. Erdey-Grúz and Wick (51) found that on lead and tantalum the Tafel equation was applicable with the *b* values = 0.2 approximately. Kabanov and Jofa (106) found the *b* value for the Tafel line of lead in aqueous acid solution = 0.116; and Lukovtsev, Levina, and Frumkin (127) found that on nickel there were positive deviations[2] from the Tafel equation in the range 10^{-8} to 10^{-6} amp./sq. cm., but from 10^{-6} to 10^{-2} amp./sq. cm. this equation was applicable with $b = 0.10$. The Russian work on lead and nickel was carried out under stringently controlled conditions, with rigorous deoxygenation of the solution and electrolytic purification. Values of overpotential under apparently comparable conditions on the same metal from independent work are often discrepant by more than 0.1 v., and this is mostly due to the purity of the electrode material and solution.

Some investigation has been made of the hydrogen overpotential on catalytically active metals at low current density ranges where the logarithmic relation would be supposed from theory to break down. Volmer and Wick (157) find an approximately linear relation between current and potential near the reversible potential on platinum, gold, and iridium electrodes.

(d) Cathodes other than mercury at high current densities

Kabanov (110) determined the hydrogen overpotential on silver from 10^{-3} to 10^{-0} amp./sq. cm. and on platinum from 10^{-3} to 10^{2} amp./sq. cm. in 5 *N* hydrochloric acid solution and obtained an apparent applicability of the Tafel equation with *b* values of 0.13 and 0.12, respectively.

In this work, no details are given with regard to cathode preparation; there is a considerable scatter of points around the Tafel line and the method of correcting for ohmic overpotential is crude.

Essentially different results were obtained by Hickling and Salt (90) on some eighteen of the more common metals in 1 *N* aqueous hydrochloric acid solution within the current density range 10^{-3} to 10^{-0} amp./sq. cm., using the commutator method and means of purifying the solution which did not include prepolarization. These workers found that the Tafel equation was applicable in the current density range studied only to comparatively few metals, i.e., bismuth, iron, nickel, tungsten, gold, and platinized platinum, whilst for other cathodes (particularly those of high overpotential) there were negative deviations from the Tafel lines which indicated an approach of the overpotential to a limiting value independent of current density. Values of the *b* factor, measured from the lower linear sections of the curves, showed that although for some cathodes $b \simeq 0.1$, a large number of exceptions existed, the range covered by the *b* factor being 0.03–0.3 approximately (see table 2).

Bockris (13) measured the overpotential on copper, lead, nickel, molybdenum, columbium, tantalum, indium, and thallium, using the direct method and the same method of preparation of the solution and same current density range as

---

[2] Namely, deviations in the sense that the values of overpotential observed were greater than those expected from the Tafel equation.

Hickling and Salt. He obtained fair agreement with the results of Hickling and Salt for copper, lead, and nickel (i.e., metals examined by the latter workers) and observed a similar kind of negative deviation from the Tafel equation for indium, thallium, and tantalum as these workers observed for lead, tin, copper, etc.

It should be noted that these deviations from the Tafel equation at high current densities have only been observed in solutions which were not electrolytically purified. Work in electrolytically purified solutions at high current densities has not yet been reported. The position is therefore still uncertain.

(e) Experimental evidence on the *b* factor

The value of the *b* factor in the Tafel equation for different metals is controversial and of great importance to the theory of hydrogen overpotential. Values of *b* obtained by different authors in aqueous acid solution at the same intermediate current density ranges are in poor agreement, as is shown in table 2 (13), where values of *b* from recent work are tabulated. The average of these values is 0.17 (or 0.14 if the result for *C* is neglected) and from this and the scatter of the values there is no clear support for the contention of some workers that *b* is a constant equal to 0.12 at 25°C. for all pure metals. Conversely, it is significant that in those few experiments where electrolytic purification of the solution and stringent elimination of oxygen have taken place, the *b* value found ≃ 0.10–0.14 at intermediate current densities. Thus, several workers have reported *b* values for lead of 0.2–0.3; but Jofa and Kabanov (106) found that in carefully purified solutions the slope of the Tafel line was 0.12. There is as yet insufficient work in highly purified solutions to be able to assess the generality of this result. A first aim of most theories of overpotential is the theoretical interpretation of *b*. The most urgently needed experimental work appears to consist in determining its value in the most carefully purified solutions and on electrodes of very high purity.

TABLE 2

Experimental values of b

METAL	*b*	METAL	*b*	METAL	*b*	METAL	*b*
Be	0.11	Cb	0.11	W	0.09	Hg	0.15
C	0.84	Mo	0.13	Pt (platinized)	0.02	Hg	0.12
Al	0.12	Rh	0.14	Pt (platinized)	0.08	Tl	0.08
Fe	0.12	Ag	0.12	Pt	0.3	Pb	0.3
Ni	0.11	Cd	0.25	Pt	0.19	Pb	0.23
Cu	0.16	In	0.25	Au	0.08	Bi	0.10
Cu	0.12	Sn	0.2	Au	0.12		

2. Effect of temperature

The principal interest in measuring the temperature coefficient of hydrogen overpotential is to obtain the energy of activation, ΔH. Two different methods may be used for the measurements (Agar (4)). The overpotential at a temperature T is measured against a reversible electrode either at the same temperature or at some other temperature, T_0. Some uncertainty is involved in the latter method, owing to thermoelectric potentials in the bridge connecting the cell to the reversible electrode. According to Agar (4) this difference between the two resulting energies of activation is of the order of 1 kg.-cal.

Values of the temperature coefficient are of the order of a millivolt per degree and the energies of activation vary from about 5 to 20 kg.-cal. in various systems. The sparse data up to 1938 are recorded by Bowden and Agar (31). Since this time little fresh data on the energy of activation has been recorded.

Information on the variation of the coefficient b with temperature is contradictory. Bowden found b proportional to T (i.e., α = constant) for mercury in 0.2 N aqueous sulfuric acid. This was confirmed by Jofa and Mikulin (108). In more concentrated acid solution, however, Jofa and Stepanova (109) found that b passed through a minimum between 0° and 80°C. Bockris and Parsons (24) observed that α increased slightly with increase of temperature in methanol solutions of hydrogen chloride. Hickling and Salt (93) found that in 1 N aqueous hydrochloric acid b decreased with temperature on some metals, e.g., tungsten. (It is also relevant to record that Stout (151) observed b constant with increasing temperature for the deposition of the azide ion, and Roiter and Jampolskaja (142) observed the same behavior of b in work on the electroreduction of oxygen.)

There is therefore little evidence to show that α is in general independent of temperature and indeed this would not be expected on theoretical grounds (24). No measurements exist in solutions containing capillary-active substances in known quantities. It would seem advantageous to extend the range of temperatures downwards by the use of non-aqueous solutions. This would be particularly useful for those metals which dissolve at higher temperatures.

3. *Effect of change of state*

An important experiment carried out by Bowden and O'Connor (33) showed that fusion of a gallium cathode caused the hydrogen overpotential at a current density of 10^{-4} amp./sq. cm. to increase considerably.

4. *Effect of pressure*

Harkins and Adams (85, 86) varied the pressure simultaneously over a mercury cathode and the reference electrode and found no effect on the overpotential. Goodwin and Wilson (80) found a decrease in overpotential on increase of pressure. Bircher and Harkins (10) repeated the work of Harkins and Adams and found that the *cathode potential* was independent of pressure, i.e., the overpotential decreased with increase of pressure. Harkins' work, of apparently excellent quality considering its early date, is confusing, as the earlier work of 1914 was published after the contradictory work of 1923.

Ipatiev (101) measured the overpotential on platinized platinum in acid and alkaline solutions with a mercurous sulfate electrode and pressures up to 100 atm. The potential of the cell was observed to increase with pressure but not in accord with the normal logarithmic relation for the dependence of potential of a reversible electrode with pressure.

Cassel and Krumbein (40) found that the cathode potential was independent of hydrogen pressure in 1 N sulfuric acid and 1 N potassium nitrate solutions. Schmidt and Stoll (145) obtained a similar result for copper, nickel, lead, and silver cathodes in $N/10$ sodium hydroxide solutions but the results for iron, zinc, and tin cathodes were somewhat irregular.

The results for mercury cathodes are particularly contradictory, and the effect of partial hydrogen pressure in hydrogen–nitrogen mixtures was examined by Bockris and Parsons (24) in $N/10$ hydrochloric acid solutions. They found the cathode potential to remain constant with change of hydrogen pressure.

For many metals, therefore, most of the evidence indicates that the cathode potential is approximately independent of pressure.

5. Effect of time

(a) Build-up

Baars (6), and at about the same time Bowden and Rideal (35), reported the overpotential during the initial passage of current to be linearly dependent upon the quantity of electricity passed. For mercury this linear relation has a constant slope for nearly its whole length. For some other metals changes in slope occur, thus indicating that the charging up of the double layer is not the only process occurring during this initial increase of potential.

After this first build-up, which in oxygen-free solutions lasts about 0.25 sec. on mercury at a current density of 2.5×10^{-4} amp./sq. cm., the overpotential undergoes some more complex changes with time on some metals ("long-time" effects) which depend markedly on the properties of the metal (13, 90). Thus, for metals of high overpotential, such as lead and mercury, there is little further variation with time after the initial "short-time" build-up. With metals of low overpotential, however, considerable changes, usually increases, occur, and the overpotential may take several hours to reach a steady state. Such variations take place also in solutions which have been very stringently deoxygenated and electrolytically purified (73, 120, 127).

(b) Decay

Isolated observations made by Bowden and Rideal (35) and by Baars (6) led to the conclusion that the rate of decay of overpotential was proportional to log t, where t is the time after cessation of the polarizing current. This was confirmed by Butler and Armstrong (39) for mercury and platinum cathodes, it being concluded from the relative rates of decay on these two cathodes that some electromotive atomic hydrogen existed on platinum, but not on mercury cathodes (at overpotentials less negative than −1 v.) during polarization in acid solution. Ferguson and Kleinhechsel (63) studied cathodes of platinum, palladium, gold, silver, zinc, cadmium, antimony, and nickel and found that the decay consisted of two parts: (*i*) a rapid potential drop completed in 0.01 sec., followed by (*ii*) a slow decay towards the reversible potential. Increasing the speed of stirring increased the rate of decay. The work of Hickling and Salt (94) somewhat confirmed that of Ferguson and coworkers. The second potential decay is initially approximately proportional to log t, as agrees with the earlier work, but deviates from this law after a few minutes. Frequent steps occur in the decay curves and these were shown—by examination of the effect of adding small quantities of the suspected salt—to be caused by trace metal impurities, deposited on the cathode, which reach their dissolution potential at the beginning of each step.

Frumkin and Aladjalowa (73) studied the build-up and decay of hydrogen overpotential on palladium in electrolytically purified solutions. These authors suggested that there is a quantitative connection between the build-up and decay processes, the fraction of the overpotential building up slowly after switching on the current being equal to the fraction decaying slowly. No such relation exists between the build-up and decay processes on a metal of high overpotential, e.g., lead, although these appear to be *qualitatively* similar to those on palladium (23).

6. *Effect of electrode material*

The dependence of the hydrogen overpotential upon the electrode material is a fundamental aspect of the phenomenon to which attention was paid by earlier workers, but which has more recently lacked emphasis. The approximate order of the metals, arranged according to their increasing hydrogen overpotential at 10^{-3} amp./sq. cm.[3] in 1 N aqueous hydrochloric acid solution, is: platinum, rhenium, gold, tungsten, molybdenum, nickel, iron, tantalum, copper, silver, chromium, beryllium, columbium, bismuth, thallium, lead, tin, cadmium, mercury.

In general, metals with high melting points have a low overpotential and *vice versa*. Further, overpotential at a given current density increases with the metal in the same order as does the metal's power of catalyzing the reaction $H + H \rightarrow H_2$ (Bonhoeffer (26)).

It was pointed out by Bockris (13, 14) that if the hydrogen overpotential at a given current density on various metals and the thermionic work functions of the metals were both plotted against their atomic numbers, the overpotential showed a periodicity of a kind opposite in sense to the thermionic work function, i.e., metals with a large thermionic work function corresponded to those with a low hydrogen overpotential and *vice versa*. This dependence is shown in figure 4, where two definite groups and one less definite group are seen. It is notable that mercury does not fit into any of these groups. Statistical analysis shows that there are three distinct lines and that the two upper lines have significantly different slopes (18).

7. *Effect of surface properties*

Most workers have made small additions to knowledge of this factor, but few studies have been devoted to it, and interpretation of past results is uncertain owing to the unknown amount of impurity introduced into the surface during preparation.

---

[3] This current density is chosen for purposes of comparison because it avoids the controversies of measurements at very high or very low current densities.

In general, roughening lowers the overpotential. Conversely, polishing (35) tends to increase it. Scraping, i.e., removing the surface layers of a soft metal such as lead, generally reduces the overpotential somewhat from that in the unscraped (i.e., usually dirty) state. Annealing in hydrogen generally seems to increase the overpotential of the metals of lower overpotential (35). The so-called anodic activation (73) of electrodes, which consists in subjecting them to a preliminary anodic prepolarization, usually causes the overvoltage to be lowered.

Surfaces prepared by electrodeposition are associated with notably different absolute values of overpotential; the variation with time during polarization is also reduced (90). It is usual to plate onto copper or platinum; Bockris and Parsons (24) showed, however, that the overpotential depended to a significant extent on the nature of the base metal for silver cathodes, so that some standard base metal, e.g., copper, must be chosen.

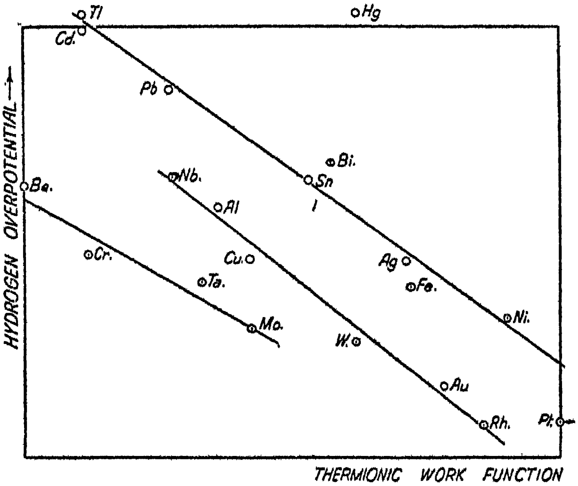


FIG. 4. Relation between hydrogen overpotential and thermionic work function

The effect of electropolishing the metal surface has been examined by Bockris and Azzam (19), who find that metals of high overpotential such as copper and lead are little affected by electropolishing but that for metals of lower overpotential, such as tungsten and nickel, electropolishing increases the overpotential by an order of about 0.1 v. at medium or high current densities.

8. Effect of diffusion through the cathode

Earlier work (e.g., particularly 47 and 130) on the transfer of hydrogen overpotential through a thin film of metal produced contradictory results, probably owing to the presence of impurities in solution which are known to affect adsorption markedly. Uhlig, Carr, and Schneider (155) found a transfer of potential after some minutes for electrodes consisting of iron–chromium alloys in partially deoxygenated sodium chloride solution. Conversely, Ferguson and Dupbernall

(62) failed to observe any transfer of overpotential through platinum and palladium plates and concluded that previous erroneous observations of a transfer had been caused by the porosity of the films to the solution by means of passage through the Smekal cracks.

Work in prepolarized solutions by Frumkin and Aladjalowa (73) showed an immediate transfer of a part of the overvoltage from the polarization to the diffusion side of a palladium electrode. The part of the overpotential transferred corresponded approximately to that component of it on palladium which varied with time (see figure 5; i. e., $\eta_{\text{transferred}}$ was found equal to $\eta_1 = \eta_1'$).

The situation with regard to this work is at present unclear. In work which avoids the undesirable presence of rubber and other adhesives for attaching the diffusion electrode to the glass of the cell it is extremely difficult to eliminate small leaks between the polarization and diffusion sides of the electrode. Frumkin and Aladjalowa attempted to overcome this difficulty by attaching the palladium electrodes to platinum and sealing this metal to glass. Work at Imperial College has shown that such seals are often the source of leaks (which give rise to transfers of a similar nature to those claimed by others) in these experiments.

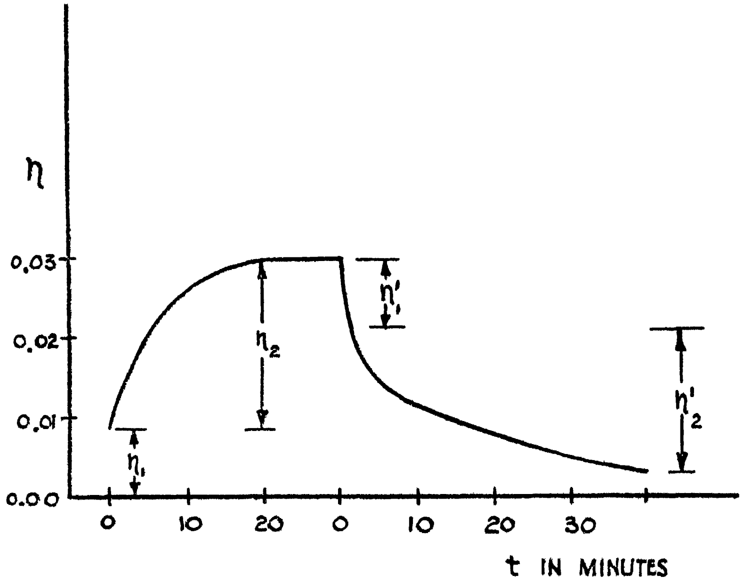


FIG. 5. Variation of overpotential with time on palladium electrode in acid solution at 10^{-4} amp./sq. cm. (73).

Experiments on the transfer of overpotential are very important because they may give direct information on the "electromotive activity" of atomic hydrogen.

It may be that diffusion of hydrogen into the metal during electrolysis is more general than is often supposed. Thus, on nickel cathodes the evolution of hydrogen continues for several seconds after cessation of the polarizing current when the current density is greater than 10^{-3} amp./sq. cm. (17).

9. *Effect of shape and curvature of cathode*

According to Sederholm and Benedicks (146) overpotential is related to the radii of curvature of a curved electrode according to the empirical formula:

$$\eta = \eta_0 + K \log\left(1 + \frac{K'}{r}\right)$$

where η_0 is the overpotential on a plane surface, K and K' are constants, and r is the radius of curvature. The relation does not appear to have received specific test by other workers.

Baars (6) reported a dependence of overpotential upon the area of the electrode, but Hickling and Salt (90) could not confirm this.

10. *Effect of alloy formation*

Fischer and Barabanov (64) showed that deviations from a simple additive law existed in amalgams of cadmium, lead, and bismuth, and Cruatto and Da Via (43) found that for lead–antimony and lead–cadmium alloys in alkaline solution the overpotential rose with increase of the content of antimony or cadmium when two phases are present; in the presence of mixed crystals there is a rapid increase of overpotential with increase in antimony for lead–antimony alloys; and for lead–cadmium a decrease with increase in cadmium.

No general conclusions can be drawn from the available data. It must be questioned whether this field can be very profitable for overpotential research; changes in the structure in the surface caused by changing ratio of the components are difficult to separate from other effects of changes of composition.

C. SOLUTION FACTORS

11. *Effect of hydrogen-ion concentration*

Earlier work, particularly that of Bowden (28), was vitiated by the presence of impurities (123). Levina and Sarinsky (123) showed that in an acid concentration from 0.001 to 0.1 *N* the overpotential remains independent of the pH on mercury cathodes. Jofa (103, 104) found that at concentrations above 0.1 *N* in hydrochloric acid the overpotential becomes less negative with increasing hydrogen-ion concentration. This decrease with increasing hydrogen-ion concentration was also observed by Béthune and Kimball (8) in sulfuric and phosphoric acid solutions up to 9.65 *M* sulfuric acid and 5.65 *M* phosphoric acid. Bockris and Parsons (24) found that in methyl alcohol solutions of hydrogen chloride the hydrogen overpotential at a dropping-mercury electrode was affected by pH change to a larger extent than that in aqueous solution and the change with concentration began at a notably higher pH than in aqueous solutions.

On metals other than mercury the situation is not yet clear. On lead, Kabanov and Jofa (106) found that the overpotential was almost independent of the pH for the range 0.01–8 *N* sulfuric acid. At higher concentrations in sulfuric acid solution, the overpotential decreases with increasing concentration. A similar change was noted in solutions of hydrochloric, hydrobromic, and perchloric acids, the changes with concentration being less than for mercury (104).

On nickel Lukovtsev, Levina, and Frumkin (127) found an independence of the pH only in the region 0.0003–0.001 *N*. At concentrations above 0.001 *N* the overpotential decreases with increasing hydrogen-ion concentration (see also Legran and Levina (121) and Sindjukov (148)).

Hickling and Salt (93) consider that for platinized platinum, tungsten, and mercury, the changes which occur upon increase of the concentration of hydrochloric acid from 0.1 *N* to 6 *N* have no fundamental significance. They observed, however, a large increase in overpotential at 10^{-1} amp./sq. cm. in 0.1 *N* hydrochloric acid solution on tungsten and platinum, a fact which they attribute to the existence of large concentration overpotential at this concentration, although it was not observed on mercury cathodes under the same concentration conditions.

Very little work has been done in alkaline solutions. On mercury cathodes it is particularly difficult, owing to the simultaneous deposition of sodium. Amalgam formation is unimportant at low current densities, according to Bowden and Kenyon (113).

12. *Effect of foreign salts*

Erdey-Grúz and Szarvas (49) measured the effect of various simple salts on the overpotential at mercury and found the mean activity of the salt (a) to be related to the overpotential in salt solution by the approximate empirical equation:

$$\eta = \eta_0 + K \log a$$

where η_0 is the overpotential in pure acid solution and K is a constant.

Levina and Sarinsky (123) examined the effect of lanthanum chloride on mercury cathodes and found that it caused a decrease in overpotential, although the slopes of the Tafel lines were not affected. Effects of low-valent halides are more complex and according to Jofa, Kabanov, Kutschinski, and Chystiakov (107) addition of potassium halide to hydrochloric acid solution decreases the a value of the Tafel equation particularly at low current densities, thus causing an inflection on the Tafel line (figure 6) (see also Kolotyrkin and Bune (119)).

On metals of low overpotential there is little data on the salt effect. Lukovtsev, Levina, and Frumkin (127) have shown that for nickel at low current densities in acid solution, lanthanum chloride causes a lowering of overpotential, but at higher current densities an increase. In alkaline solutions, a small lowering is produced in dilute solutions which becomes zero in concentrated solutions.

13. *Effect of solvent*

The first examination of the solvent effect under suitable experimental conditions was made by Levina and Silberfarb (124), who found that at a low current density on mercury a lowering of overpotential took place in alcoholic when compared with aqueous solutions. The b value remained unchanged. This was confirmed by Novoselski (134). Bockris and Parsons (24) examined the solvent effect on mercury cathodes at low and intermediate current densities in $N/10$ methanolic hydrochloric acid and the corresponding methanol-water mixtures. The *b* values decrease up to 0.3 mole fraction of alcohol. At constant current density there is, on addition of methyl alcohol, an initial lowering of overpotential, which then remains constant until high alcohol concentration, when it again falls to the value in pure methanol solution, which is about 0.14 below that in aqueous solution. Similar results were observed at dropping mercury electrodes. Hickling and Salt (91) measured the overpotential on mercury at high current densities in solutions of hydrogen chloride in ethylene glycol, ethyl alcohol, and cylcohexanol. Contrary to the uniform results of the above authors, these workers found the overpotential to be greater in the non-aqueous than the aqueous solutions.

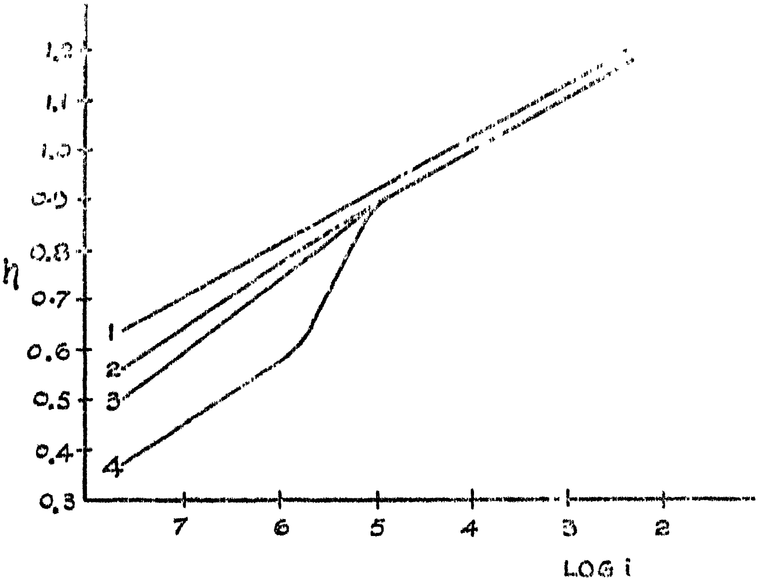


FIG. 6. Effect of salts on hydrogen overpotential. Curve 1, N Na_2SO_4 + 0.1 N H_2SO_4; curve 2, N KCl + 0.1 N HCl; curve 3, N KBr + 0.1 N HCl; curve 4, N KI + 0.1 N HCl.

Hickling and Salt (91) also examined the solvent effect on lead, tin, tungsten, platinum, and lead at high current densities and found here also an increase with change of solvent. This result is probably due to the presence of sealing wax as a fixative for cathodes in the systems of those workers: its dissolution would cause a poisoning effect. Bockris *et al.* (12, 15, 23, 24) carried out an investigation of the solvent effect on lead, tin, copper, and nickel cathodes, using solutions of 1 N hydrochloric acid in the solvents methyl and ethyl alcohols, glycol, formic and acetic acids, ether, dioxane, and, where practical, a complete range of mixtures of these with water. In general it appears that on the metals of high overpotential—lead, tin, and, to a lesser extent, copper—there tends to be a decrease of overpotential in the non-aqueous solvents which was greatest for methyl alcohol and least for ethylene glycol solutions, whilst on nickel the overpotential was little changed or somewhat increased. More complex effects occurred in mixed solvents, in which the overpotential passed through a maximum at intermediate composition in some systems. Measurements of the overpotential on twelve metals over the range 10^{-3} to 10^{-1} amp./sq. cm. in a 1 *N* solution of hydrogen chloride in methyl alcohol showed that on metals of low overpotential little change in *a* or *b* occurred; on metals of medium overpotential *b* was slightly decreased and *a* increased; and on metals of high overpotential *a* was decreased.

Pleskov (139) measured the hydrogen overpotential on nickel, mercury, and lead in liquid ammonia at −50°C., but the results must be considered to be largely vitiated owing to the presence of visible films formed during electrolysis on the electrode surface of the last two metals. Results on nickel are difficult to compare with those in aqueous solution, owing to the large temperature differences involved.

14. Effect of catalytic poisons and activators

Several isolated studies of the effect of additives on overpotential have been carried out but systematic work is lacking. Kobozev and Nekrasov (118) found that mercurous chloride or hydrogen sulfide increased the hydrogen overpotential on platinum cathodes. Volmer and Wick (158) found that small amounts of arsenic trioxide brought about a lowering of overpotential on a platinum cathode, the *b* value in Tafel's equation being also lowered; higher concentrations, however, caused an increase in *a* and *b*. Knorr and Schwartz (117) found that arsenic trioxide raised the *b* value for a platinum cathode at all concentrations, which is the generally accepted result (see Von Naray-Szabo (160)). Varisikova and Kabanov (156) carried out an extensive study of the effect of additives on a spongy lead cathode in 2.8 *N* sulfuric acid. They found that alkylammonium derivatives were particularly effective in raising the hydrogen overpotential. Hickling and Salt (93) observed increases on mercury, tungsten, and platinized platinum cathodes caused by additives of carbon disulfide, arsenic trioxide, and mercuric chloride.

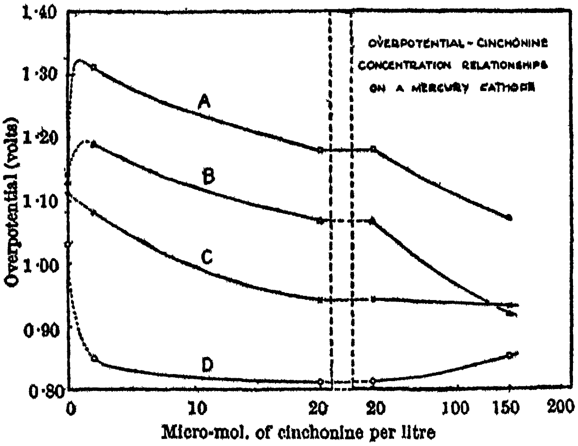
The converse phenomenon of additives which lower the overpotential is a rarer one. Semerano (147) observed that some alkaloids changed their polarographic half-wave potentials for the discharge of hydrogen from aqueous acid solutions to more positive values, and Bockris and Conway (20) found that certain alkaloids of the quinoline group caused a lowering of overpotential on mercury. The effect was decreased on tungsten and inverted on platinized platinum (see figure 7).

The situation in this field suffers particularly from a lack of systematic work on various cathode materials and correlation of the concentration of the additive with its activity. A connection between the structure of the additive and the threshold concentration at which the overpotential is affected should be obtained. Study of the dependence of activating or poisoning action on the structure of the additive, and adsorption measurements on poisoned electrodes, are necessary.

An interesting application of the study of poisons on hydrogen overpotential is in the field of inhibitors of acid corrosion. Bockris and Conway (22) have shown, by measurements of overpotential on iron cathodes by direct and commutator methods in solutions containing certain organic bases, that the presence of these inhibitors raises the true hydrogen overpotential. The mechanism of partial inhibition of the acid dissolution of iron is hence by a direct effect on the hydrogen overpotential and not by means of the mechanical protection of an adsorbed film, as had been suggested (42).

15. Effect of gaseous depolarizers, e.g., oxygen

In spite of frequent qualitative observations in the literature, few authors have undertaken quantitative work on the action of oxygen on hydrogen overpotential. Hickling and Salt (92) examined the effect of additions of oxygen to a solution containing a mercury (amalgamated copper) electrode: at current densities above 10^{-3} amp./sq. cm. they found that the overpotential was almost independent of the amount of oxygen present, although this had a very considerable effect at current densities below 10^{-3} amp./sq. cm. Bockris and Azzam (19) found that oxygen still had a marked lowering effect (about 0.15 v.) on the overpotential at a current density of 10^{-3} amp./sq. cm. at a liquid mercury electrode and that the current density above which the effect of oxygen became negligible varied somewhat with the cathode material.



A, 10^{-1} amp./sq. cm.; *C*, 10^{-3} amp./sq. cm.
B, 5×10^{-2} „ „ ; *D*, 10^{-5} „ „ .

FIG. 7. Effect of cinchonine on hydrogen overpotential

The effect of gaseous depolarizers other than oxygen does not seem to have been studied.

16. Effect of colloids

No recent measurements of the effect of colloids on overpotential appear to be recorded in the literature. Older work indicates an increase of overpotential on addition of colloidal material (128, 141).

17. Effect of radiation

Bowden (30) showed that the hydrogen overpotential on a mercury cathode was reduced by ultraviolet light. The threshold frequency was 4000 Å. and the effect depended on the potential. Preliminary attempts (133, 138) have also been made to examine the effect of supersonic waves on overpotential, but it seems likely that the small effects observed were caused by resultant decreases in concentration overpotential.

In a field yielding direct quantitative information on the kinetics of the reaction at the cathode, more work might have been expected. A comparison of the effect of light on cathodes evolving hydrogen and oxygen (the transfer of electrons here being activated in an opposite direction) would be of particular interest. A difficulty which might be expected in the experimental technique is that of heating effects, which may obscure the very small changes in potential due to light effects.

IV. The Theory of Hydrogen Overpotential

A. GENERAL EQUATIONS AT A WORKING HYDROGEN ELECTRODE

1. Definition of currents at cathode and anode

Suppose that $\vec{v}$ is the velocity of the reaction:

$$2H^+ + 2e \rightarrow H_2$$

and $\overleftarrow{v}$ that of the reaction:

$$H_2 \rightarrow 2H^+ + 2e$$

Then $F(\vec{v} - \overleftarrow{v})$ may be called the *net cathodic current*, i_c:

$$i_c = F(\vec{v} - \overleftarrow{v}) \tag{1}$$

Correspondingly, the net anodic current, i_a, is:

$$i_a = F(\overleftarrow{v} - \vec{v}) \tag{2}$$

From equations 1 and 2:

$$i_c = \vec{i} - \overleftarrow{i} \tag{3}$$

$$i_a = \overleftarrow{i} - \vec{i} \tag{4}$$

where the quantities $\vec{i}$ and $\overleftarrow{i}$ may be termed the *cathodic and anodic current*, respectively.

At equilibrium, $i_c = i_a = 0$

$$\vec{i} = \overleftarrow{i} = i_0 = \textit{the exchange current} \tag{5}$$

2. The Tafel equation

For the reaction

$$2H^+ + 2e \rightarrow H_2$$

let it be assumed, for conditions under which $\overrightarrow{v} \gg \overleftarrow{v}$, (*1*) that the velocity of the rate-determining stage is controlled by a process which can be undergone only by particles having more than some minimum (activation) energy and that such particles are Maxwellianly distributed; and (*2*) that the energy of activation of the reaction is affected by the electric field of the cathode by an amount proportional to some part $(E - X)$ of the metal solution potential difference, where E is the potential difference of the metal solution and X may depend on the condition of the electrode surface, or the properties of the solution, etc. Let the proportionality factor for this effect of the cathode field be α.

Hence:

$$i = Ae^{-[U+(E-X)\alpha F]/RT} \tag{6}$$

where U is the "thermal part" of the energy of activation of the reaction and A is a collision factor characteristic of the mechanism of the reaction; A may depend on the concentration of some entities in the solution near the electrode and/or on the electrode surface.

$$E = K + X - \frac{RT}{\alpha F} \cdot \log_e i \tag{7}$$

But $\eta = E - E_r$, where E_r is the potential of a reversible hydrogen electrode under the same conditions, except for flow of current, as those for the irreversible electrode.

$$\eta = \left(K + X - \frac{RT}{F} \log_e a_{\text{H}^+}\right) - \frac{RT}{\alpha F} \log_e i \tag{8}$$

Or,

$$\eta = a - b \log_e i \tag{9}$$

where a is a term dependent in the general case on pH and $b = RT/\alpha F$.[4] Hence, assuming only a Maxwellian distribution of the particles governing the slow stage of the reaction and an effect on the energy of activation proportional to some part of the cathode potential, overpotential is found to be logarithmically related to current density. It is stressed that no particular mechanism of overpotential is assumed in this deduction.

3. The reaction $2\text{H}^+ + 2e \rightarrow \text{H}_2$ *at the working hydrogen electrode: principal theories of hydrogen overpotential (16)*

If the solvent molecule with which the hydrogen ion is solvated is represented by B and the cathode material by M, the following are possible reaction paths occurring during the electrolytic evolution of hydrogen:

$\text{BH}^+ + e \rightarrow \text{B} + \text{MH}$; $\text{BH}^+ + \text{MH} + e \rightarrow \text{H}_2(\text{gas})$

$\text{BH}^+ + e \rightarrow \text{B} + \text{MH}$; $\text{BH}^+ + \text{MH} \rightarrow \text{BH}_2^+\text{M}$; $\text{BH}_2^+ + e \rightarrow \text{H}_2(\text{gas}) + \text{B}$

$\text{B} + \text{B} + e \rightarrow \text{MH} + \text{BO}^-\text{B}$; $\text{MH} + \text{MH} \rightarrow \text{H}_2(\text{gas})$

$\text{BH}^+ + e \rightarrow \text{B} + \text{MH}$; $\text{MH} + \text{MH} \rightarrow \text{H}_2(\text{gas})$

---

[4] Numerical values of b quoted in this work are always to $2.303RT/\alpha F$.

Various stages in these reaction paths have been assumed to be rate determining, which assumptions give rise to the theories of hydrogen overpotential. Those of modern interest are set out below:

ORIGINAL AUTHORS	A: MAIN THEORIES	NAME OF MECHANISM
Smits (169)......	$BH^+ + e \rightarrow B + MH$	Slow discharge
Horiuti (96).....	$BH_2^+ + e \rightarrow B + H_2$	Molecular hydrogen ion
Eyring (157)....	$B + B + e \rightarrow MH + (B\text{-}H)^- + B$	Prototropic transfer
Tafel (153)......	$MH + MH \rightarrow H_2 + 2M$	Catalytic
Horiuti (99).....	$BH^+ + MH + e \rightarrow H_2(gas) + B + M$	Electrochemical
	B: DUAL THEORIES	
Kobozev (118)..	$MH + MH \rightarrow H_2(gas) + 2M$ $BH^+ + MH + e \rightarrow B + H_2(gas) + M$	Catalytic–electrochemical
Frumkin (69)....	$BH^+ + e \rightarrow B + MH$ $BH^+ + MH \rightarrow H_2(gas) + B + M$	Slow discharge–electrochemical

For a review of older theories, see reference 7. The above equations are incomplete expressions of the various theories and do not indicate the detailed mechanism of reaction.

The processes occurring at a cathode during the electrolytic evolution of hydrogen involve (*i*) the transport of the solvated ion BH^+ to a position in the double layer at the electrode–solution interface, where it can be regarded as adsorbed; (*ii*) neutralization of the proton, either by (*a*) electron transfer to the proton or (*b*) proton transfer to the electron-donating surface of the metal; (*iii*) desolvation of the proton; (*iv*) adsorption of hydrogen atoms produced in stage (*ii*) on the cathode surface; (*v*) desorption of the hydrogen atoms by (*a*) catalytic combination or (*b*) combination with a proton and an electron to form hydrogen molecules.

The above processes at the cathode can be divided into two parts: (I) the processes *ii*, *iii*, and *iv*; and (II) the processes *v*. Processes *ii*, *iii*, and *iv* constitute the discharge of hydrogen ions,—namely, the production of adsorbed hydrogen atoms from solvated protons or solvent molecules; processes *v* constitute the combination of hydrogen atoms and/or ions to form molecules.

Theories of hydrogen overpotential can therefore be divided into two ill-defined groups according to whether the rate-determining process is the *discharge* of hydrogen ions or the *combination* of entities on the electrode surface.

The principal modern contributions to the slow discharge theories can be divided into four subgroups.

(*1*) *General slow discharge theory* (*Frumkin* (*66*, *67*, *71*)): In this theory, the discharge reaction $BH^+ + e \rightarrow MH$ is treated as a single process without detailed consideration of processes *ii*(*a*), *ii*(*b*), *iii*, or *iv* of the above. Frumkin states (66) that his version of the slow discharge theory does not distinguish between *ii*(*a*) or *ii*(*b*).

(*2*) *The* (*energy level*) *slow discharge theory* (*Polanyi* (*100*); *Butler* (*37*)): The discharge reaction is considered without reference to a detailed mechanism but conditions for discharge are worked out energetically with reference to the molecular properties of proton, solvent, and metal.

(*3*) *Molecular hydrogen ion* (*Horiuti* (*96*)): According to this mechanism, the rate-controlling process is the neutralization of the H_2^+ (or BH_2^+) ion formed by combination of BH^+ with MH.

(*4*) *Prototropic transfer* (*Eyring* (*57*)): In this theory, the rate-determining step is the *transfer* of a proton from a *solvent molecule* in solution to a solvent molecule attached to the cathode surface. It is clear that this mechanism involves the discharge of hydrogen ions, as defined above; hence it is grouped under the heading "slow discharge."

The general slow discharge theories are ambiguous. Thus, it is claimed (2) that the processes of neutralization, desolvation, and adsorption take place simultaneously, so that no distinction can be made between them. This latter statement may be true at present, but there is no reason why the energetics of these different stages should not be considered in detail. Ambiguity also exists concerning the postulate that proton or electron transfer is rate determining. The general slow discharge theory may be subdivided into the groups: (*i*) slow neutralization (66, 67, 71), involving those theories in which neutralization by an electron can be regarded as the rate-determining reaction; and (*ii*) slow transfer, involving those theories in which proton transfer (37, 100) and prototropic transfer (57) are regarded as slow stages. The usefulness of this subdivision is lessened by the lack of clear definition of the slow stages postulated by Frumkin (66, 67, 71) and by Butler (37).

The main combination theories are divisible into two groups, in each of which there are treatments which differ only in detail.

(*1*) *Catalytic combination* (*Tafel, 153*), *Kobozev* (*118*), *Horiuti* (*99*), *Hickling* (*95*)): The rate-determining step is the second-order reaction between adsorbed hydrogen atoms.

(*2*) *Electrochemical mechanism* (*Horiuti* (*99*), *Frumkin* (*67*)): The rate-determining reaction is that between a solvated proton (BH^+), an adsorbed hydrogen atom, and an electron.

The concept of dual theories originated with Kobozev and Nekrasov (118), although this fact does not seem to be generally recognized. A dual theory may be defined as one in which the rate of the over-all reaction $2BH^+ + 2e \rightarrow H_2(\text{gas})$ is controlled by two processes having velocities of the same order and occurring simultaneously on the electrode surface.

For the general equation for the reaction $2H^+ + 2e \rightarrow H_2$ in which all of the above mechanisms are taken into account, see Bockris (16).

B. THE SLOW DISCHARGE THEORIES

1. *General slow discharge theory*

(a) Essential theory

Smits's (149) suggestion in 1924 that neutralization was a slow stage in the evolution of molecular hydrogen was developed quantitatively by Erdey-Grúz and Volmer (50) in 1930 on the evidence of the charging curve data of Baars (6) and of Bowden and Rideal (35), which were not explicable on the Tafel mechanism. Erdey-Grúz and Wick (51) allowed for a non-symmetrical energy barrier at the electrode–solution interface in this treatment.

Gurney (83) developed the theory quantum-mechanically, supposing neutralization to take place by tunnel electrons at some distance from the cathode (see Fowler (65) for a review of this work). Gurney's theory is now rejected because: (*i*) Topley and Eyring (154) showed that the mechanism leads to energies of activation much higher than those observed; (*ii*) according to it, overpotential should be independent of the cathode material and its surface properties. Actually, overpotential at constant current density decreases with increasing work function of the metal (13, 14, 16) and depends markedly on surface properties. These latter objections do not necessarily apply to other slow discharge theories, some of which yield interpretation of the latter factors from the assumption of adsorbed hydrogen atoms on the electrode surface.

The above theories indicated that hydrogen overpotential depended on the pH; this is not so in dilute solution at mercury cathodes. Frumkin (66) avoided this difficulty by taking into account the difference in hydrogen-ion concentration in the bulk of the solution and in the electrical double layer. Assuming (*i*) that Stern's theory (150) of the double layer is valid, and (*ii*) that the solutions are dilute, then:

$$(C_{\mathrm{H}^+})_{\mathrm{D.L.}} = (C_{\mathrm{H}^+})e^{-\psi F/RT} \tag{10}$$

$$\psi = \psi_0 + \frac{RT}{F}\log_e C_{\mathrm{H}^+} \tag{11}$$

where $(C_{\mathrm{H}^+})_{\mathrm{D.L.}}$ is the hydrogen-ion concentration in the double layer, (C_{H^+}) that in the bulk, and ψ the potential at one ionic radius from the electrode surface, relative to the bulk. This was taken initially to be approximately the same as the electrokinetic potential.[5]

Equation 10 is correct if the solution near the cathode surface is far from saturation with hydrogen ions, which is usually so for negative polarizations, as follows from a calculation from the known capacity of the mercury–solution interface under these conditions (66).

Let E be the potential of the working electrode at a given current density. Then, if only the potential across the Helmholtz section of Stern's double layer is effective in controlling the rate of ionic neutralization at the electrode surface:

$$\overrightarrow{i} = k_1(C_{\mathrm{H}^+})_{\mathrm{D.L.}}e^{-[\alpha_1(E-\psi)F]/RT} \tag{12}$$

---

[5] Equation 11 is a rough approximation from Stern's theory. Equations 10 and 11 are

Similarly:

$$\overleftarrow{i} = k_2(C_{\mathrm{H}})e^{[\alpha_2(E-\psi)F]/RT} \tag{13}$$

where C_{H} is the concentration of hydrogen atoms at the electrode, k_1 and k_2 are rate constants, and α_1 and α_2 are constants the meaning of which is not clear.

If $E = E_r$, the reversible potential, equation 5 is true.

Evaluation of E_r from equations 5, 12, and 13 and comparison with Nernst's thermodynamic equation for E_r shows that:

$$\alpha_1 + \alpha_2 = 1$$

In general, if the rate of the neutralization reaction is i_c amp./sq. cm. of cathode surface, then:

$$\begin{aligned} i_c &= \overrightarrow{i} - \overleftarrow{i} \\ &= k_1(C_{\mathrm{H}^+})_{\mathrm{D.L}}\, e^{-[(E-\psi)\alpha_1 F]/RT} - k_2(C_{\mathrm{H}})e^{[(E-\psi)\alpha_2 F]/RT} \end{aligned} \tag{14}$$

At sufficiently high current densities $\overrightarrow{i} \gg \overleftarrow{i}$. Hence, from equation 14 and the equation for E_r:

$$\eta = \text{const.} - \frac{RT}{\alpha_1 F}\log_e i_c - \left(1 - \frac{1}{\alpha_1}\right)\frac{RT}{F}\log_e C_{\mathrm{H}^+} + \left(1 - \frac{1}{\alpha_1}\right)\psi \tag{15}$$

Therefore, assuming equation 11:

$$\eta = \text{const.} - \frac{RT}{\alpha_1 F}\log_e i \tag{16}$$

For very low current densities the second term in equation 14 becomes appreciable and causes the Tafel line to become asymptotic to the log current density axis. The conclusion that at low current density overpotential is proportional to current density cannot be made from Frumkin's versions of the general slow discharge theories.

From equation 15 pH change has no effect on overpotential in pure solutions. This result depends upon the use of equation 11, which is inexact, and the more basic assumption that ionic adsorption potentials can be neglected. If an excess of neutral salt is added, ψ is a constant and hence at constant current density:

$$\eta = \text{const.} - \left(1 - \frac{1}{\alpha}\right)\frac{RT}{F}\log_e (C_{\mathrm{H}^+}) \tag{17}$$

where the constant term is independent of pH.

For addition of neutral salts at constant pH and current density from equation 15:

$$(\eta + \psi) = \text{const.} \tag{18}$$

(b) Development of the general theory of slow discharge

Essin (55) generalized the theory in the form given by Erdey-Grúz and Volmer (50) by taking into account activity coefficients and concentration overpotential.

Recent developments have been mainly concerned with the interpretation of pH and salt effects on overpotential at higher acid concentrations.

In this connection, Jofa and Frumkin (105) attempted to allow for the effect of ion–solvent interaction in the double layer. These authors add to the energy of the transition state, equivalent in the elementary theory to $(\alpha(E - \psi) + \psi)F$, a term correcting for the difference in the activity coefficient of the hydrogen ion in the transition state to that in the bulk which occurs owing to changes in solvation at the electrode surface. Thus, the energy corresponding to the above term now becomes: $(\alpha(E - \psi) + \psi)F + RT \log_e f_T - RT \log_e f_{\mathrm{H}^+}$, where f_T and f_{H^+} are activity coefficients of the hydrogen ion in the transition state and the bulk, respectively.

Hence:

$$i_c = k_1 \frac{f_T}{f_{\mathrm{H}^+}} (C_{\mathrm{H}^+})\, e^{-[(\alpha(E-\psi)+\psi)F]/RT} \tag{19}$$

Let

$$f_T = f_{\mathrm{H}^+}^{(1+\alpha')} \tag{20}$$

$$i_c = k_1 C_{\mathrm{H}^+} f_{\mathrm{H}^+}^{\alpha_1} e^{-[(\alpha(E-\psi)+\psi)F]/RT} \tag{21}$$

Whence:

$$\eta = \text{const.} - \frac{RT}{\alpha F} \log_e i + \left(\frac{1 - \alpha}{\alpha}\right) \frac{RT}{F} \log_e C_{\mathrm{H}^+} + \left(\frac{\alpha'}{\alpha} - 1\right) \frac{RT}{F} \log_e f_{\mathrm{H}^+} - \frac{(1 - \alpha)}{\alpha} \psi \tag{22}$$

If equation 11 is applicable, the variation of overpotential with pH can depend only on f_{H^+}. This is improbable, for if f_{H^+} is varied with constant anion content (e.g., in hydrochloric acid–potassium chloride mixtures) the overpotential remains constant. Further, changes in overpotential with pH found on mercury cathodes are dependent on the cathode potential, so that anions are probably present in the double layer (105). Hence, changes with pH arise mainly from the inapplicability of equation 11 in concentrated solution.

Of considerable interest to the slow discharge theories is the recent work of Fedotov (58) who showed, by means of capacities calculated from decay curves, that for mercury the usually accepted value of the double-layer capacity (18–20 μF/sq. cm.) is retained over the current density range 5×10^{-5} to 5×10^{-3} amp./sq. cm., i.e., at quite high overpotentials. This indicates that over this range of current densities there is no change in the amount of atomic hydrogen on the mercury surface. Frumkin (72) considers that this implies absence of hydrogen atoms from the surface of mercury polarized under these conditions, so that a slow combination mechanism cannot be important on mercury cathodes.

(c) Fundamental aspects of the general slow discharge theory

There is good qualitative agreement between this theory and experiments on mercury cathodes. In particular, a reasonable, though only qualitative, explanation of salt and pH effects is given. The following difficulties arise:

(*i*) The coefficient α receives no special interpretation (*cf.* Horiuti and Polanyi (100)), and the value of $\alpha = \frac{1}{2}$ is purely experimental and has no theoretical basis. On the basis of some other theories, however (e.g., that of Eyring (57) or Hickling (95)), a reasonable theoretical estimate can be given for α.

(*ii*) The theory does not lead to calculation of correct numerical values in contrast to other mechanisms (96, 99, 135).

(*iii*) The effect of adsorption of hydrogen atoms on the discharge process is undefined. On metals of high overpotential it appears that adsorbed hydrogen is supposed to be absent from the metal surface (*cf.* Frumkin's (72) conclusions to Fedotov's work, etc.) The theory is not then consonant with the connections between surface properties, work function, etc., and overpotential on other metals of high overpotential.

(*iv*) Discharge of many ions proceeds without marked overpotential. It is unclear why discharge of protons should be a slow stage.

2. The (energy level) slow discharge theory

Horiuti and Polanyi (100) first considered the discharge of protons ("proton transfer," according to these authors) in the light of energy level diagrams. They assumed adsorption of the hydrogen atoms formed from the discharged proton and were the first authors to point out that the state of adsorption of these could affect the rate of proton discharge so that the experimental connection between properties of the metal surface and overpotential became understandable without assuming necessarily that a surface-catalyzed reaction was rate determining.

Butler (37) developed the views of Horiuti and Polanyi and those of Gurney. The energy required to remove an electron from the lowest energy level of a hydrogen atom is the ionization potential, I. Electrons may hence pass from the cathode material to an adjacent hydrogen ion if $\phi < I$, where ϕ is the thermionic work function of the metal. In solution, the stabilizing solvation energy (L) and the repulsion energy (R) between water and the hydrogen atom must be taken into account, so that $\phi < I - L - R$ becomes the condition for neutralization. This is true if a zero potential difference exists at the metal–solution interface. If this potential difference is V, $\phi + Ve < I - L - R$ is the condition for neutralization. If the metal is one of low overpotential, the adsorption energy of hydrogen atoms on the metal is also added, so that $\phi + Ve < I - L - R + A$.

The condition for discharge can be illustrated by a plot of potential energy against distance (figure 8). AA represents the curve of L, the interaction energy of a proton and water raised by a distance corresponding to I; BB represents the curve of R raised vertically by $\phi + Ve$. To combine the latter curve with a curve representing A to obtain a curve representing $\phi + Ve + R - A$, the distance between the center of the water molecule and that of a metal atom in the cathode is assumed to be the sum of the radii of these entities. CC represents the combined curves of $R - A$ raised by a distance corresponding to $\phi + Ve$.

Suppose C^1C^1 represents $\phi + Ve - R + A$ for the electronic level $\phi - \Delta\phi$; then the probability of finding an electron in this level is proportional to $e^{-\Delta\phi/RT}$. As C^1C^1 intersects AA at X^1, an electron in the level $\phi - \Delta\phi$ can neutralize an ion in the energy level E corresponding to X^1. The probability of an ion having this energy is $e^{(E_0-E)/RT}$.

Hence:

$$i = \int_{E_0}^{E} e^{(E_0-E)/RT}\, e^{-\Delta\phi/RT} \text{ const. } dE \tag{23}$$

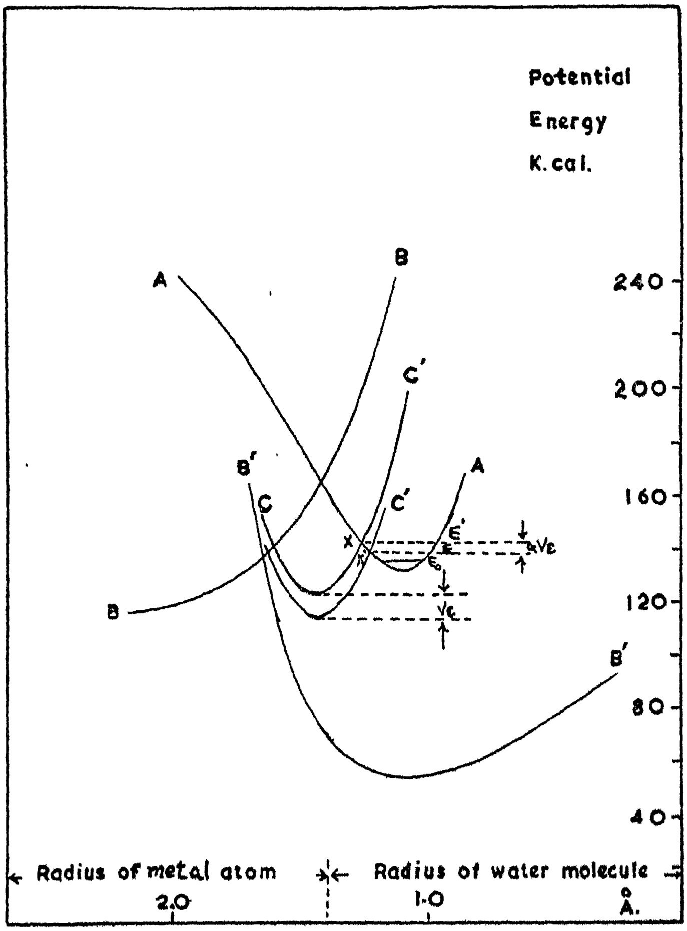


FIG. 8. Plot of potential energy against distance

But

$$\Delta\phi = -\frac{m_C - m_A}{m_A}(E^1 - E) = \frac{1}{\alpha}(E^1 - E), \quad \text{say.} \tag{24}$$

$$i. = \int_{E_0}^{E} e^{(E_0-E)/RT}\, e^{(E^1-E)/\alpha RT} \text{ const. } dE \tag{25}$$

Whence, with the relation

$$\frac{dE^1}{e\,dV} = \alpha \tag{26}$$

the equation

$$V = a^1 - \frac{RT}{\alpha F}\log_e i \tag{27}$$

is obtained.

The slow discharge theory as given by Butler is particularly useful in providing a model for proton discharge. The following ambiguities exist: (*i*) the rate-determining stage implied is unclear; (*ii*) there is no attempt to deal with the effect of concentration factors and the structure of the electrical double layer. If V is assumed to be the absolute cathode potential and a concentration term is introduced into the equation for the current, then an incorrect dependence of overpotential on concentration is obtained (24). A rigorous kinetic treatment of the energy level slow discharge theory would be valuable.

3. Hydrogen molecule ion theory

Horiuti, Okamoto, and Hirota (96) suggested that the rate-determining stage at metals of high hydrogen overpotential was the neutralization of the BH_2^+ ion. This mechanism is analogous to the general theory of slow discharge. Attention has therefore been directed to gaining support for the suggestion of the existence of H_2^+ near a cathode during the evolution of hydrogen.

Consider a simple Helmholtz double layer, of capacity C.

$$-CE = \epsilon(n_{H^+} + n_{H_2^+}) \tag{28}$$

where E is the absolute electrode potential, ϵ the electronic charge, and n_{H^+} and $n_{H_2^+}$ the numbers of H^+ and H_2^+ present per square centimeter of the electrode surface. Hence, the charge necessary to create a unit area of new surface is

$$q = \epsilon(n_{H^+} + 2n_{HH^+}) \tag{28a}$$

n_{H^+} and $2n_{H_2^+}$ are calculated as a function of potential by consideration of the equilibrium

$$B(H_2^+) \rightleftharpoons (H)_{Ads} + BH^+ + \epsilon$$

so that at equilibrium

$$F\eta = RT\log_e\frac{n_{H_2^+}}{n_{H^+}C_{H^+}} + C' \tag{29}$$

where C' is a constant.

Calculation of the charging current as a function of η on this basis (i.e., assuming the existence of H_2^+) agrees quantitatively with experimental results obtained by the authors with dropping-mercury electrodes, though these are somewhat at variance with the results of other workers. α is shown to be given by the relative inclination, at the point of intersections of the potential energy–distance relations for H^+ and H_2^+ and, when repulsion on the mercury surface is allowed for, turns out to be 0.6 in quite good agreement with experiment.

This theory is based upon an apparently reasonable quantitative calculation, unlike the theory considered above. However, direct experimental support, which is based upon one type of measurement, must be considered to be slender.

It may be noted that an H_2^+ ion also appears in Heyrovsky's theory (87), which is based mainly upon polarographic data. Here, it arises from the combination of H_{Ads} with a solvent molecule:

$$MH + H\text{—}OH \rightarrow H_2^+ + OH^-$$

No direct support for the existence of the H_2^+ ion is given.[6]

4. Slow prototropic transfer theory

(a) Essential theory

The theory of absolute reaction rates was applied by Eyring, Glasstone, and Laidler (57) to hydrogen overpotential as follows: If α is the fraction of the overpotential which affects the velocity of the rate-determining reaction at the electrode surface in the direction of cathodic discharge (figure 9), then:

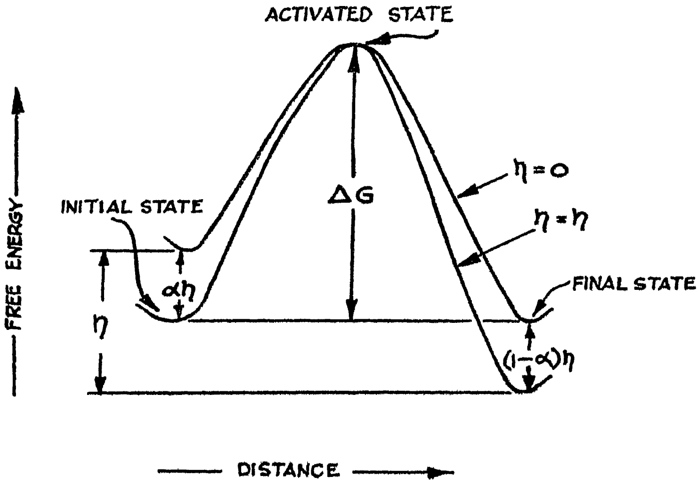


FIG. 9

$$i_c = \frac{F}{N}\left[C_1\frac{kT}{h}e^{-[\alpha\eta F+\Delta G_1^{\ddagger}]/RT} - C_2\frac{kT}{h}e^{[(1-\alpha)\eta F-\Delta G_2^{\ddagger}]/RT}\right] \tag{30}$$

where C_1 and C_2 are the concentrations of the reacting entities in the rate-determining processes controlling the cathodic and anodic currents, respectively.

When

$$i \gg i$$

$$\eta = \frac{RT}{\alpha F}\log_e\frac{FC_1kT}{Nh} - \frac{\Delta G_1^*}{\alpha F} - \frac{RT}{\alpha F}\log_e i \tag{31}$$

---

[6] Difficulties exist in the interpretation of polarographic data on overpotential, mainly owing to the lack of information on current density in this work (75).

Or:

$$\eta = a - \frac{RT}{\alpha F} \log_e i \tag{9}$$

where a is a constant, independent of pH.

When η is so small that the term for the reverse process in equation 30 becomes appreciable, then

$$\eta = -\frac{NhRT}{F^2 C_1 kT} e^{\Delta G_1^{\ddagger}/RT} i \tag{32}$$

assuming that $C_1 = C_2$, $\Delta G_1^* = \Delta G_2^*$, and $\eta < 0.03$ v.

These general equations can now be applied to evaluating the slow stage of the reaction.

If $\eta = 0$, and $i = i_0$,

$$i_0 = \left(\frac{F}{N} C_1 \frac{kT}{h} e^{\Delta S^*/R}\right) e^{-\Delta H/RT} \tag{33}$$

or

$$i_0 = Be^{-\Delta H^*/RT} \tag{34}$$

where

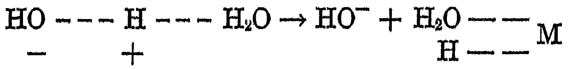
$$B = \left(\frac{F}{N} C_1 \frac{kT}{h} e^{\Delta S^*/R}\right) \tag{35}$$

The quantity i_0 is obtained by extrapolation from results on overpotential at low and medium current densities and ΔH can be calculated from a knowledge of the temperature coefficient. Hence, B is obtained from equation 35.

The authors conclude from a small number of experimental values of ΔH that B is substantially a constant independent of the cathode material or the pH of the solution. Exceptions are considered to be due to some extraneous factors, e.g., amalgam formation during hydrogen evolution on mercury cathodes in alkaline solution. It therefore follows that C_1 and ΔS are constant, i.e., that the concentration of the rate-determining entity is constant and independent of pH. This entity must therefore be water, which must therefore be involved in the rate-determining reaction.

It is postulated that the cathode is covered with a layer of water molecules, adjacent to which is another layer of water molecules, associated with the solution. The slow reaction is the transfer of a proton from a water molecule of the solution layer to one on the electrode layer, i.e.,

Solution —— H_2O H_2O —— Metal →



$$\underset{-}{\mathrm{HO}} - - - \underset{+}{\mathrm{H}} - - - \mathrm{H_2O} \rightarrow \mathrm{HO^-} + \begin{matrix}\mathrm{H_2O} - - \\ \mathrm{H} - - \end{matrix}\,\mathrm{M} \tag{36}$$

C_i, the number of water molecules per square centimeter on the electrode surface, is approximately 10^{15}. ΔS may be roughly estimated, because from the above it is clear that the limiting process is similar to the ionization of water and therefore the change in entropy should be of the same order, i.e., approximately −34 cal./gram-mole. Calculation of B with these values of C_1 and ΔS and the usual values of the other constants in equation 35 gives a value of the same order as the values calculated from experimental results by means of equation 34.

(b) Fundamental aspects of the slow prototropic transfer theory

This theory has the advantage of an apparently quantitative basis for its fundamental postulate. α is the fraction of ηF effective between the initial and the activated states of the discharge reaction and this leads with moderate logic to the value of $\frac{1}{2}$ for α.

Frumkin (69) has criticized the postulate that a layer of water molecules is attached to the cathode. It is difficult to assess the likelihood of this concept. Schaaf (144) concluded from observations of the effect of the vapor of water and alcohols on the thermionic emission from platinum that there was reversible physical adsorption but no chemical adsorption. Cassel and Salditt (41) found that at non-polarized interfaces with mercury, the adsorption of vapor was not primarily dependent on the dipole moment of the molecule but rather on its size and molecular refractivity (e.g., benzene was strongly adsorbed and water not at all). This evidence seems to be against a chemisorbed layer of water molecules attached to the electrode but it applies to non-polarized interfaces of the solid–gas type. At a polarized solid–liquid interface it seems unlikely that molecules of a strongly polar solvent would not orient themselves perpendicularly to the negatively charged cathode and even if no chemisorption occurred, this electrostatic attachment would meet the requirements of the model. It is relevant to note that the H/D conversion is poisoned by the presence of water on the catalyst (48).

The probable existence of a cathode and a solution layer of solvent molecules does not necessarily imply a symmetrical fall of potential from cathode to solution, upon which the value $\alpha = \frac{1}{2}$ is based. According to modern theories of the electrical double layer a diffuse section is present, and there seems no *a priori* reason to suppose that the potential governing the reaction at the cathode should act only over the non-diffuse portion. Further, it seems unlikely that the two solvent layers of the slow prototropic transfer theory should be strictly symmetrical, because on the solution side the molecules must take their places in the pattern of the solvent whilst on the cathode side they presumably act more as single entities. The explanation of the value $\alpha = \frac{1}{2}$ therefore seems to be oversimplified.

A more fundamental difficulty concerns the significance of η in equation 30 and following equations. η is assumed to be the overpotential but this is obviously incorrect, the kinetics of the rate-determining reaction at the cathode being a function of the cathode–solution potential difference. This difficulty, and also the fact that the type of double-layer structure assumed at the cathode–solution interface differs from that which is successful in explaining a number of other (particularly electrokinetic) phenomena at electrode–solution interfaces, has been discussed by Kimball, Glasstone, and Glassner (114). They continue to regard η as the overpotential, and consequently have to postulate two different double layers at the electrode–solution interface, possessing two different energy barriers over which the proton must pass. The barrier nearest to the electrode is the higher and the overpotential is therefore established essentially across this inner layer, whilst variations in equilibrium potential caused by changes in hydrogen-ion concentration are established across the outer layer. Quantitative development of this is complex and uncertain. If proton discharge is assumed to be the slow stage, η is a function of pH, but if protropic transfer is slow, η is independent of pH. The latter mechanism is therefore accepted. No account is taken of the changes in the structure of the double layer with pH, nor of ion–solvent interaction in the double layer. In discussions of η in this connection (38, 114) it was not realized that overpotential generally varies with pH and is independent of it as an exception The discussion concerning the significance of η in equation 30 thus appears misguided.

TABLE 3

Dependence of B on pH

SYSTEM	*B*	SYSTEM	*B*
Hydrogen overpotential			
Hg/0.2 *N* H_2SO_4	1×10^2	Hg/0.1 *N* NaOH	2×10^{-2}
Ga/0.2 *N* H_2SO_4	3×10^2	Pt (bright)/0.1 *N* NaOH	4×10^{-2}
Wood's metal/0.1 *N* H_2SO_4	1×10^3	Hg/0.2 *N* D_2SO_4	2×10^{-3}
Cu/*N* HCl	4×10^2	Pb/*N* HCl	3×10^0
Pt (bright)/0.2 *N* H_2SO_4	2×10^2	*Oxygen overpotential**	
Pd/0.2 *N* H_2SO_4	1×10^3	Pt/0.2 *N* H_2SO_4	5×10^2
		Pt/0.1 *N* NaOH	1×10^0

* An advantage of the slow prototropic transfer theory is that it yields an interpretation of oxygen overpotential by a reversal of the mechanism for hydrogen overpotential described above. *B* values calculated from oxygen overpotential should be the same and are therefore given here.

There are at present insufficient data (3, 29, 36, 97, 108, 111, 152) to allow of a definite estimation of the dependence of *B* on pH. In table 3 available results for various systems are given.

From these values there is little justification for the claim of the authors that *B* is constant and independent of the pH of the solution, as most of the "constant" values are in solutions of the same pH.[7] Moreover, Butler (38) has shown that if in place of the equation

$$i_0 = Be^{-\Delta H^*/RT}$$

---

[7] The values for mercury in 0.1 *N* sodium hydroxide are included here, it having been shown by Bowden and Kenyon (113) that amalgam formation is not important for this system at low current densities.

the equation

$$i_0 = (C_{\mathrm{H}^+})B'e^{-\Delta H^*/RT}$$

is written, a slightly more constant value of B' is obtained than B.

Temperature coefficient data are available (108, 109) in concentrated hydrochloric acid solution for mercury cathodes over the concentration range 1–10 N. B values calculated from these results vary from 10^{-6} to 10^{5}. The theory is therefore definitely incorrect in concentrated acid solution (17).

The acceptance at present of the slow prototropic transfer view as a general theory of overpotential is prevented by several difficulties. However, the *method* of attack presents advantages over others and as further data concerning i_0, ΔH^*, and ΔS^* become available, it may be possible by this approach to make a convincing estimate of the slow stage effective for a given system.

C. SLOW COMBINATION THEORIES

1. *Catalytic theory*

The catalytic mechanism has been treated in two fundamentally different ways. It is possible to assume the applicability of the classical thermodynamic relations between electrode potential and concentration of "electromotively active" material, and, by correlating the concentration of the latter with the current, obtain a relation between η and current density. Or, purely kinetic methods may be used with the assumption of some effect of the electrode potential on the reaction rate. These two methods can be termed respectively the "quasi-thermodynamic" and the "kinetic" catalytic theories.

(a) Quasi-thermodynamic catalytic theory

(i) Essential theory

Tafel (153) considered the slow combination between two hydrogen atoms on the electrode surface to govern their surface concentration. The atomic hydrogen was assumed to be electromotively active, i.e., the electrode potential became more negative with increasing concentration of adsorbed atomic hydrogen. An equation analogous to the Nernst equation for the relation between reversible potential and ionic activity was assumed to apply, so that if n and n_r are the number of hydrogen atoms per square centimeter on an electrode across which passes a current density i_1 and on the reversible hydrogen electrode, respectively, then, neglecting the anodic current:

$$E - E_r = \eta = \frac{RT}{F} \log_e \frac{1}{n} \qquad (37)$$

But $i = kn^2$, if the reaction MH + MH → H_2 is of the second order.[8] (38)

---

[8] The order of the reaction should be 2 or 1, according to whether the slow combination is MH + MH → H_2(gas) or MH + H → H_2(gas).

Hence

$$\eta = a - \frac{RT}{2F} \log_e i \tag{39}$$

where a is a constant at constant T. (40)

The theory has an obvious interpretation of the relation between the electrode material and overpotential: namely, that the overpotential is low for metals of good catalytic power and high for poor catalysts.

Equation 39 is clearly incorrect, because its b factor $= RT/2F$. In equation 38 if the order of the reaction is taken to be x, then $b = RT/xF$. If $b = 0.12$, $x = \frac{1}{2}$, a result which is improbable.

Two serious difficulties are met in Tafel's original theory: (*1*) the b value of the Tafel equation is one found for few metals; (*2*) there is no experimental foundation for applying the thermodynamic equation for electrode potentials to *adsorbed* hydrogen, although it is known to be valid with respect to gaseous hydrogen at reversible electrodes. To avoid the first difficulty, it has been suggested (77) that the concentration of the hydrogen atoms outside the electrode surface should be connected to the concentration of those adsorbed on it by an adsorption isotherm. This gives $b = mRT/F$, where m is about 1–6, so that a large range of experimentally observed values of b is satisfactorily interpreted. (If m be taken as 1–10, a range which is reasonable at an electrified interface, $b = 0.03$–0.30 approximately.)

Hickling and Salt utilize essentially this method of accounting for b and express the electrode potential equation in terms of atomic hydrogen pressures, which are considered to arise as a result of the presence of (dissolved ?) atomic hydrogen at a pressure p_H.

Hence

$$E - E_r = \eta = -1.98 - \frac{RT}{F} \log_e p_H \tag{41}$$

where -1.98 is the standard electrode potential of the atomic hydrogen electrode.

Also,

$$i = k_1 n^2 \quad \text{and} \quad n = k_2 p_H^{1/m} \tag{42}$$

where k_1 and k_2 are constants. Therefore:

$$\eta = a - \frac{mRT}{2F} \log_e i \tag{43}$$

where a is a constant, at constant T, independent of pH.

For high current densities, when a certain degree of saturation of the electrode surface has been reached, Hickling and Salt suppose that an increasing proportion of the hydrogen evolution at the cathode takes place by the electrochemical mechanism. Further increase in current density then results in no further increase in adsorbed atomic hydrogen, so that p_H, and therefore the overpotential, become constant (*cf.* the experimental position, page 536).

The theory of Hickling and Salt gives a satisfactory qualitative description of the effect of many "electrode factors" but is less useful in the treatment of solution factors, e.g., pH change. It retains the chief advantage of Tafel's theory—reasonable interpretation of *a*—and offers a more rational account of *b* than most other theories.

However, the pressure of atomic hydrogen corresponding to the overpotential of 1 v. according to this theory is $10^{-16.9}$ atm. and assuming the liberal depth of 100 layers of gaseous atomic hydrogen, this pressure is equivalent to about 10^{-4} atoms over each square centimeter of electrode surface (11). Such an anomalous concentration can hardly be explained on the grounds that it is a stationary concentration of rapidly moving atoms, for if z atoms per second pass through unit area travelling at x cm./sec., the concentration of atoms is $\frac{z}{x}$ atoms/cc. But if the current is i, $z = iN/F$; hence the concentration of atomic hydrogen is iN/xF per cubic centimeter. This should be approximately equal to 10^2 atoms/cc., which is the amount per cubic centimeter corresponding to the 10^{-4} atoms in the volume described above (i.e., for a mercury electrode at 10^{-3} amp./sq. cm.). Hence $x = 10^{13}$ cm./sec. (136). These results suggest that the literal physical meaning attributable to Hickling and Salt's model is limited.

(ii) Fundamental aspects of the quasi-thermodynamic catalytic theory

A considerable difficulty in these theories is the use of thermodynamic equations to represent the potential of electrodes on which the processes are not at equilibrium. The use of isotherms such as that of Freundlich is open to criticism on similar grounds.

The assumption of electromotive *atomic* hydrogen, in the theories of Tafel (153) and of Hickling and Salt (95) in the adsorbed and the dissolved state, respectively, is made without direct evidence. There is also little treatment of the double layer in these theories, so that it is not possible to express overpotential as a function of "solution factors."

Conversely, the slow combination theories described above provide a satisfactory qualitative model for the interpretation of overpotential (particularly "electrode factors") and related phenomena (e.g., electrolytic reduction). Their correct formulation does not seem possible upon a quasi-thermodynamic basis.

(b) Kinetic catalytic theory

This has been developed by Okamoto, Horiuti, and Hirota (99) for a nickel cathode by a detailed theoretical treatment, using the transition state method and taking account of the repulsive forces between the hydrogen atoms on the nickel surface.

The limiting condition for the existence of this mechanism on a given metal is clearly the level of the lowest adsorption state (*cf.* Topley and Eyring (154)). Upon the assumption that the adsorbed hydrogen is practically non-polar, application of the transition state method to the reaction MH + MH → H_2 shows that

$$\text{Rate of combination: } V = KGe^{-\epsilon_{H_2}/kT}\,\frac{1}{P^2} \tag{44}$$

$$\text{Rate of atomization: } V' = KGe^{-\epsilon_{H_2}/kT}\,\frac{n}{Q_{H_2}} \tag{45}$$

where G is the number of adjacent pairs of metal atoms at which atomization or combination occurs, ϵ_{H_2} is the minimum potential energy of H—H in the activated state, and n is the number of hydrogen molecules per unit volume.

$$Q_{H_2} = \frac{(2\pi mkT)^{3/2}4\pi^2\,IkTe^{-\epsilon_{H_2}/kT}}{h^5 \sinh \dfrac{h\nu_{H_2}}{2kT}} \tag{46}$$

$$K = \frac{kT}{h}(1 - \theta)^2 e^{-u^*\theta/kT} \sum_{j=0}^{j=1\text{-}5} \frac{1}{2} \sinh \frac{h\nu_{H_2,i,j}}{2kT} \tag{47}$$

$$q = e^{(\epsilon_{H^+}+u\theta)/kT} \sum_{j=0}^{j=1\text{-}5} \left(\frac{1}{2} \sinh \frac{h\nu_{H_2}}{2kT}\right) \tag{48}$$

$$\frac{1-\theta}{\theta} = \sqrt{\frac{\dfrac{Q_{H_2}}{n}}{q}}\, e^{FE/RT} \quad \text{and} \quad P = \sqrt{\frac{Q_{H_2}}{n}}\, e^{FE/RT} \tag{49}$$

where θ = the degree of saturation of chemisorbed atoms; $\epsilon_{H_2} = -109.12$ kg.-cal.; $\nu_{H_2,i,j}$ = 936, 87, 1704, 368, 626 cm.^{-1} = normal vibration frequencies of H—H in the activated state; $\nu_{H,i,j}$ = 417, 479, 1900 cm.^{-1} = normal vibration frequency of hydrogen in the adsorbed state; ν_{H_2} = 4417.2 cm.^{-1} = harmonic frequency of a hydrogen molecule; $I = 4.65 \times 10^{-41}$ gram-cm.^2 = moment of inertia of hydrogen molecule; u = 5.65 kg.-cal. = repulsive potential of adsorbed hydrogen due to surrounding hydrogen when $\theta = 1$; u^* = 6.70 kg.-cal. = repulsive potential of H—H in the activated state due to surrounding chemisorbed atoms.

The steady cathodic current is found to be:

$$i = 2KGe^{-\epsilon_{H_2}/RT}\left(\frac{1}{P^2} - \frac{n}{Q_{H_2}}\right) \tag{50}$$

Tests of this expression have been carried out on nickel electrodes by calculating from it and from the interchange reaction, G, and then comparing this with z, the number of available metal atoms per square centimeter for chemisorbed atomic hydrogen. The three values obtained are 4×10^{-14}, 2×10^{-14}, and 2×10^{-14}, respectively. Direct calculations of i are also in fair agreement with experiment at low current densities and α is calculated to be 0.7 (experimental value for nickel = 0.6 in acid solution).

Criticism may be made chiefly on the ground that, from this mechanism, limiting current density would be expected at fairly low current density. This has not been observed. The assumption that the metal–hydrogen bond is nonpolar is also doubtful, and if it is assumed to have a reasonable dipole moment the calculated value of α is erroneous (70).

Conversely, the theory yields quantitatively correct values of overpotential on nickel at low current densities and is the most comprehensive attempt at a rigorous quantitative kinetic theory of hydrogen overpotential hitherto made. The approach invites much further work.

2. *Electrochemical theory*

It was first suggested by Kobozev and Nekrasov (118) that the rate-controlling step at working hydrogen electrodes was under certain conditions the combination of solvated hydrogen ions with adsorbed hydrogen atoms and an electron to form gaseous molecular hydrogen. Horiuti and Okamoto (96) also utilized this mechanism. A concise treatment is given by Frumkin (67) as follows:

Let ψ be momentarily assumed equal to 0, C_{H^+} be the number of hydrogen ions adsorbed on the surface, n = the number of adsorption centers on the surface, and E the cathode potential.

The following reactions (i, ii, and iii) take place:

$$\mathrm{BH^+} + e \rightarrow \mathrm{MH} \tag{i}$$

The rate of this process is given by

$$R_1 = k_1\left(1 - \frac{C_{\mathrm{H}}}{n}\right) C_{\mathrm{H}^+} e^{-EF/2RT} \tag{51}$$

where C_{H^+} is the hydrogen-ion concentration in the bulk of the solution (and therefore, if $\psi = 0$, at the electrode surface). The author is followed here in assuming without theoretical justification that $\alpha = \frac{1}{2}$.

$$\mathrm{MH} \rightarrow \mathrm{BH^+} + e \tag{ii}$$

The rate of this process is:

$$R_2 = k_2 \frac{C_{\mathrm{H}}}{n} e^{-EF/2RT} \tag{52}$$

$$\mathrm{MeH} + \mathrm{BH^+} + e \rightarrow \mathrm{H_2} \tag{iii}$$

$$R_3 = k_3 \frac{C_{\mathrm{H}}}{n} - C_{\mathrm{H}^+} e^{-EF/2RT} \tag{53}$$

In the stationary state, therefore, we have that

$$k_1\left(1 - \frac{C_{\mathrm{H}}}{n}\right) C_{\mathrm{H}^+} e^{-EF/2RT} - k_2 \frac{C_{\mathrm{H}}}{n} e^{EF/2RT} - k_3 \frac{C_{\mathrm{H}}}{n} C_{H^+} e^{-EF/RT} = 0 \tag{54}$$

whence:

$$\frac{C_{\mathrm{H}}}{n} = \frac{k_1 C_{\mathrm{H}^+}}{k_1 C_{\mathrm{H}^+} + k_2 e^{EF/RT} + k_3 C_{\mathrm{H}^+}} \tag{55}$$

Also, according to the present assumption that reaction iii is the slow stage, we have that:

$$i = 2Fk_3 \frac{C_{\mathrm{H}}}{n} \; C_{\mathrm{H}^+} e^{-EF/2RT} \tag{56}$$

Let now C'_{H}/n be the concentration of atomic hydrogen on the electrode surface corresponding to equilibrium between hydrogen ions and atoms at a given potential E. Then

$$k_i\left(1 - \frac{C'_{\mathrm{H}}}{n}\right) C_{\mathrm{H}}\, e^{-EF/2RT} = k_2 \frac{C'_{\mathrm{H}}}{n}\, e^{EF/2RT} \tag{57}$$

Hence

$$\frac{C_{\mathrm{H}}}{n} = \frac{k_i C_{\mathrm{H}^+}}{k_1 C_{\mathrm{H}} + k_2 \cdot e^{EF/RT}} \tag{58}$$

For weak cathodic polarization

$$k_2 e^{EF/RT} > k_1 C_{\mathrm{H}^+} \tag{59}$$

and hence:

$$\frac{C_{\mathrm{H}}}{n} = \frac{C'_{\mathrm{H}}}{n} = \frac{k_1}{k_2} C_{\mathrm{H}^+} e^{-EF/RT} \tag{60}$$

From this and equation 56

$$i = 2F \frac{k_1 k_3}{k_2} C^2_{\mathrm{H}^+} e^{-3EF/2RT} \tag{61}$$

For stronger polarization

$$i = 2F \frac{k_3 k_1}{k_1 + k_3} C_{\mathrm{H}^+} e^{-EF/2RT} \tag{62}$$

for which result the converse condition to that of expression 59 is taken.

Introducing the ψ potential in equation 62 and transforming:

$$\eta = k_4 + \frac{RT}{F} \log_e C_{\mathrm{H}^+} - \psi - \frac{2RT}{F} \log_e i \tag{63}$$

where

$$k_4 = \frac{2RT}{F} \log_e 2F \frac{k_1}{k_1 + k_3} \tag{64}$$

is the absolute hydrogen electrode potential at unit activity.

The electrochemical mechanism has a satisfactory qualitative approach to most phenomena in hydrogen overpotential because it is essentially a combination of a general type of slow discharge and catalytic theories. Quantitatively, however, the agreement with experiment is unsatisfactory, e.g., it does not well interpret the pH and salt effects found by Legran and Levina (121) on nickel cathodes.

D. MISCELLANEOUS THEORIES

The older theory that a gas film of "contact resistance" at the electrode–solution interface is the cause of overpotential has received recent support from Porfirov (140) and Newbery (132).

Lemarchands and Juda (122), Phomotov (137), Bonnemay (27), and Karpen (112) have also contributed recent theoretical work which does not fall into the divisions made above.

E. DISCUSSION

1. Quantities relevant to hydrogen overpotential and open to quantitative determination[9]

Much of the past work on hydrogen overpotential has been vague, qualitative, and irrelevant to theoretical interest. *Quantitative* results of use as a numerical test of various theories should clearly be the aim of experiments. A summary of these follows:

(*a*) *α and the exchange current:* Changes of α are particularly important in giving information on *changes* of mechanism. Thus, for mercury cathodes, the value of α is approximately 0.5 in acid solution and 0.25 in alkaline solution (113), indicating the mechanism to be different in these two systems. It is possible, but unproved, that considerable deviations of α from 0.5 in aqueous acid solutions indicate the presence of impurities, particularly for high overpotential metals. i_0 gives a measure of the velocity of the reaction $2H^+ + 2e \rightarrow H_2$ at zero overpotential and provides a standard of comparison for this velocity on various metals.

(*b*) *λ, the net charge:* It can be shown (16) that if:

$$\lambda = \frac{RT}{Fi_0}\left(\frac{\partial i}{\partial \eta}\right)_{i=0} \tag{65}$$

then λ is the net number of charges which cross the energy barrier during the elementary process in the reaction at the cathode. Determination of λ is hence diagnostic. Equation 65 is valid only if $\eta < 10$ mv. approximately; the determination of overpotential at current densities low enough for this is very difficult for metals of high overpotential.

(*c*) *Limiting current density:* The existence of a limiting current due to hydrogen activation overpotential, not concentration overpotential, would be expected from the catalytic theory. This limiting current may be differentiated from one due to concentration effects by (*i*) varying the concentration of the electrolyte, which would leave any limiting current due to activation overpotential relatively unchanged (19) (so long as the concentration is not changed sufficiently to alter the mechanism of the reaction) and (*ii*) examining several metals under the same conditions of high current density, when the limiting current due to activation overpotential would be expected to be different in each case.

(*d*) *Temperature coefficient and energy of activation:* Determination of the energy of activation is of well-known importance in the determination of the mechanism of any reaction; it is of great cogence as a test of suggested mechanisms. Thus, the existence of *free* atomic hydrogen in solution near an electrode surface is improbable because the energy of activation for the overpotential is 5–20 kg.-cal./gram-mole. at the reversible potential, whereas the formation of free atomic hydrogen needs about 50 kg.-cal./gram-atom (4).

---

[9] In this and the following section only leading references are given.

Further, the energies of activation combined with i_0 yield numerical values of B of equation 36, and thus a quantitative test of the prototropic transfer theory (19).

(*e*) *pH and salt effects:* Knowledge of these factors is useful because of the relations between the electrokinetic potential and overpotential which follow from the general slow discharge theories. In alkaline solutions, a difference in direction of the salt effect follows from the general slow discharge and slow protrotropic transfer theories (4).

(*f*) *Decay:* Measurement of the decay of overpotential after cessation of the polarizing current yields information on the presence of adsorbed hydrogen on the surface of the cathode material. Its presence causes the slope of the overpotential–log time relation to be $< b$ of the Tafel equation (39).

(*g*) *Solvent effect:* Change of solvent from water to methyl alcohol, for example, affects the overpotential in a manner characteristic of the cathode material; the effect is quantitatively related to the slow discharge views and can therefore be used as a test of them. Change from a hydroxylic to, say, an ethereal solvent would cause considerable alteration in overpotential according to the slow prototropic transfer theory, owing to the absence of hydrogen bonding in the latter solvent (11).

Other quantitative electrochemical measurements, useful in elucidating the mechanism of the reaction of hydrogen evolution, are as follows:

(*h*) *Rate of single stages of the reaction at working hydrogen electrodes:* On cathodes of very low overpotential it is possible to determine separately the rate of the discharge reaction $BH^+ + e \rightarrow H + B$ as distinct from the rate of the over-all process of hydrogen evolution. Thus, on platinum in hydrochloric acid and sodium hydroxide solutions, the rate of the discharge process was considerably faster than that of the over-all process (45).

(*i*) *Capacity of the electrode–solution interface:* Measurements of capacities at the electrode–solution interface by various appropriate methods yield the following type of information: (*a*) D.C. transients can be used in conjunction with a cathode ray oscillograph for the determination of electrode capacities compared with that of mercury, which is supposed to have an ideal, smooth surface. By a not very certain argument (35), a comparison of the capacities, measured under the same conditions, of various metals per apparent square centimeter gives a measure of the ratio: true area/apparent area.

(*b*) Measurements of the capacity of the electric double layer with mercury or gallium and liquid alloys give clear information concerning anionic adsorption, which causes a shift in the electrocapillary curve in the anodic branch (78).

(*c*) Measurements of electrode capacity at various frequencies give information on the adsorption of hydrogen or other entities on the electrode. Thus, if adsorbed hydrogen atoms are present, increasing frequency allows the hydrogen atom less time to arrange itself completely, so that the apparent capacity becomes less (53). Some evidence of adsorbed material can also be obtained from D.C. transients, where the initial linear section of the potential–time relation represents the charging up of the double layer, whilst the second is concerned with the adsorption of hydrogen atoms on the metal (52).

2. Matters of contemporary interest in the interpretation of experimental results

(*a*) *Current density:* The deviations from the Tafel equation at low current density, where the Tafel line becomes asymptotic to the log current density axis, and, over a certain range and on certain metals, the overpotential becomes approximately proportional to current density, can be directly interpreted on the basis of the principal theories. Possible deviations at high current densities are of greater interest. According to slow discharge views the Tafel equation should be applicable up to indefinitely high current density. According to the slow combination views, deviations should occur at current densities high enough to cause the surface to approach saturation. In Horiuti's catalytic theory this leads to positive deviations (owing to a limiting current caused by saturation at the surface) and in Hickling's catalytic theory to negative deviations from the Tafel equation (owing to participation of an electrochemical mechanism at high current density). Unfortunately, the experimental information is not yet available to test these very diagnostic theoretical expectations. It is definite that negative deviations occur at high current density, though it is not yet proved whether they persist in sufficiently purified solutions. If they do, either a change in mechanism at higher current density must be effective or the deviations may be connected with hydride formation; it is significant that where the negative deviations are most pronounced (i.e., on cathodes such as tin and lead) the tendency to form *gaseous* hydrides is most marked. It is also significant that some solid cathodes at which the deviations from linearity in the Tafel line occur, do not retain their original bright surface after electrolysis (19). The observed deviations may be due to the deposition of impurities. Should it be established that the Tafel equation is generally applicable even at very high current density, the slow combination mechanism could be discarded for this current density range. Conversely, should the coefficient b of the Tafel equation prove to be constant at all current densities above the lowest, then this itself is a puzzling fact, because it seems reasonable to expect some deviations from a constant value over large ranges in current density, according to all existing theories.

Four principal interpretations of α have been given: (*i*) as a factor representing the relative inclinations to the horizontal of the potential energy/distance relation of the hydrogen ion in solution and the adsorbed hydrogen atom (37); (*ii*) as the fraction of the potential of the cathode effective in influencing the rate of reaction

57[10]; (*iii*) as the order of the slow combination reaction (79); (*iv*) as the experimental coefficient in the Freundlich isotherm applied to hydrogen atoms very near to and adsorbed upon the electrode surface (95). The second and last of these interpretations have been shown to lead to rational values in agreement with experiment. In much theoretical work, α is tacitly assumed equal to $\frac{1}{2}$. The limitation $\alpha < 1$ follows from the first two interpretations, and as these are associated respectively with the energy level slow discharge and slow transfer theories it can be definitely concluded unambiguously that these theories are not applicable to electrodes for which $\alpha > 1$ (e.g., platinum).

Values of b over the range 0.03–0.3 approximately are observed for various metals at intermediate current densities and successful theories must clearly be capable of giving interpretation to these values, even if the scatter of values is shown to be due to impurities in the solution. The method of establishing the Tafel line probably influences b, owing to diffusion of atomic hydrogen into metals of low overpotential, which may have effect in slow measurement.

In summary, no clear generalizations concerning the mechanism of overpotential can yet be made from the variation in current density in pure solution, owing to lack of satisfactory work at very low and very high current densities. For metals for which $b < 0.058$, however, the slow discharge theories cannot be applicable.

(*b*) *Temperature:* The behavior of the constant α with temperature is of great interest. Although α may be constant for mercury cathodes with variation of temperature in aqueous solution, there is an increase in α with increase of temperature on metals of lower overpotential (e.g., tungsten). This behavior indicates the presence of adsorption on the cathode as an important factor in determining overpotential. Formally, if α is proportional to T (i.e., b constant), the change in potential affects the entropy but not the heat of activation (4).

(*c*) *pH and salt effects:* Quantitative agreement with Stern's theory regarding the electrokinetic potential at various concentrations is not achieved by the general slow discharge theories even in quite dilute solutions. It is possible that Stern's theory as used in these calculations (i.e., in an approximated form), and also inherently, is inadequate (9).

The effect of changes in pH and the effect of salts do not appear to be diagnostic for the slow discharge theory, as seems to have been generally considered, for the electrochemical theory can also be formulated with equations of the same form as that of the general slow discharge theory. Also pH and salt effects could probably be understood according to the catalytic theory if the polar nature of the metal–hydrogen bond were taken into account.

(*d*) *Time:* The linear build-up of overpotential during the first few tenths of a second after commencement of the polarizing current is strong evidence in favor of the slow discharge mechanisms. This linear build-up, however, does not occur on metals of low overpotential. Hickling (89) attempted to reconcile the linear build-up of overpotential on metals of high overpotential with the slow combination theories by showing that the quantity of electricity needed to charge up the double layer was vastly more than that needed to establish an overpotential of 1 v., assuming that this overpotential is established according to the theory of this author. It has been shown above that this theory gives rise to results which lack physical meaning, so that this explanation of the linear increase of overpotential with time seems unsound.

---

[10] (*i*) and (*ii*) are analogous but not identical.

The slower variations with time which occur after the charging up of the double layer is completed could be interpreted in terms of the slow discharge theory as due to the setting up of certain adsorption equilibria. The nature of such equilibria in pure solutions of non-capillary-active substances is unclear. The gradual reduction of a film of oxide by the evolved hydrogen is also a possible explanation of long time variations, particularly decreases with time. These explanations seem weak when applied to the large changes with time which occur for some metals, e.g., tantalum. It is significant that the variation with time depends upon the preparation of the electrode surface. This fact is not in consonance with an interpretation of time variation depending entirely on the deposition of impurities. According to slow combination theories, changes with time are a consequence of the "deactivation" of the "active centers" of the metal with use (161). Diffusion of hydrogen into the metal is probably also a cause of time changes, from which the noted lesser variation with time on electrodeposited metals, where the thin films of cathode material give little scope to the diffusion process, would follow. Both diffusion and deactivation theories agree with the facts that time variations are more extensive with metals of low overpotential.

Metals divide themselves into two rough classes with respect to long time variations: those of high overpotential, where the initial build-up of overpotential is linear with the amount of electricity passed and the variation after the first fraction of a second's polarization is small; and those of lower overpotential, where the build-up is not totally linear with the quantity of electricity passed and the final steady value of overpotential is not reached for some time.

(*e*) *Surface:* Activation of the surface of metal electrodes causes a decrease in overpotential, as would follow were the chief purpose of the metal that of a catalyst. Aging of the surface of the metal also causes an increase in the overpotential which leads to the same implication as the result of activation. The effects of electropolishing correspond to what would be expected from a slow combination viewpoint for the metals of low overpotential. Finally, the large increase in overpotential which occurs on melting gallium tends to indicate that here overpotential involves a catalytic phenomenon depending upon the "active center" present in a solid lattice.

Surface effects are in general satisfactorily interpreted according to the viewpoint of slow combination.

(*f*) *Transfer by diffusion:* If overpotential is transferred from the polarization to the diffusion side (where there is no incoming current) of an electrode, two conclusions can be drawn: (*i*) that there is a considerable concentration of atomic

TABLE 4

Experimental criteria for the determination of fundamental reaction mechanisms at a working hydrogen electrode

THEORY	α	λ	LIMITING CURRENT	B (VARIATION WITH pH)	pH EFFECT (IN PURE SOLUTION AND ON ADDITION OF SALT)	SOLVENT EFFECT	TRANSFER OF η BY DIFFUSION THOUGH THIN FILMS	EFFECT OF p_{H_2}
Atomic hydrogen.	$0<\alpha<2$	2	Present	Varies	No effect	Depends on size of solvent molecules and their adsorption on cathode; for metals of low overpotential, increased in alcoholic solution	Present	Decrease of p_{H_2} makes more negative
Slow discharge....	$0<\alpha<1$	1	Absent	Constant for given metal	No effect in pure solution except at very high concentrations; in the presence of salt, less negative with decrease of pH	In alcoholic solution: lowered for metals of high overpotential. No effect for metals as platinum, nickel, etc., according to Butler's theory. Slightly lowered in alcoholic solutions according to Volmer and Frumkin	Absent	Same as above
Molecular hydrogen ion.........	$0<\alpha<1$	2	Absent	Varies	Same as above	Same as above	Absent	Same as above
Electrochemical..	$0<\alpha<\frac{3}{2}$	2	Absent	Varies	Same as above	Same as above	Present	Same as above
Prototropic transfer........	$0<\alpha<1$	1	Absent	Constant for all metals	No effect in pure solution; in presence of salt, unclear	Increased in alcoholic solution; large change expected in non-hydroylic solvents	Absent	No effect

hydrogen adsorbed on the surface of the working electrode (polarization side); (*ii*) that adsorbed atomic hydrogen must be electromotively active.

(*g*) *Experimental criteria for the elucidation of fundamental reaction mechanisms at a working hydrogen electrode:* A tabulated summary of some experimental results expected according to the main theories is given in table 4.

V. SUMMARIZING REMARKS

1. Experimental work of a high standard on hydrogen overpotential is still lacking except for mercury. Accurate experimental information for a number of cathode materials is particularly needed on the following factors: (*i*) current density, particularly at very low and very high current densities; (*ii*) temperature; (*iii*) pH. Transfer of overpotential through metallic films and experiments on rates of single stages are also particularly important.

2. Slow discharge is not the general mechanism of hydrogen overpotential on various metals. The most important evidence supporting this conclusion arises from pH effects on metals of low overpotential, from the transfer of overpotential through metallic films, and by experiments on the individual velocities of various reactions at the cathode. On mercury cathodes, a slow discharge mechanism seems probable in acid solution. The detailed mechanism is still uncertain.

On metals of low overpotential, some form of slow combination mechanism seems probable.

3. It is unlikely that one mechanism of hydrogen overpotential is effective for all metals. The future task consists in a detailed examination of overpotential at the more important cathode materials to establish the mechanism individually, investigation being made of distinguishing factors such as those in table 4.

4. The theory of adsorption at solid–liquid interfaces and the detailed structure of the electrical double layer would repay extensive work. Detailed information regarding the diffusion of hydrogen through metals and the kinetics of the reactions of hydrogen on solid surfaces (particularly the energy of activation of these processes) would be of great use.

Some of the work which has been described above as necessary to further advances in the field of hydrogen overpotential is in progress at Imperial College.

The author's thanks are due to Drs. H. H. Bandes, D. D. Eley, A. Hickling, and R. Parsons for helpful suggestions, and to Messrs. Azzam, Conway, Fleischmann, Ignatowicz, Kaminsky, and Thurley, through whose work and help the writing of this review became possible.

VI. REFERENCES

(1) ADAM: *The Physics and Chemistry of Surfaces*, p. 174. The Clarendon Press, Oxford (1941).
(2) Reference 1, p. 332.
(3) AGAR: Dissertation, Cambridge University, 1938.
(4) AGAR: Faraday Society Discussion on Electrode Processes, 1947.
(5) ARMSTRONG AND BUTLER: Trans. Faraday Soc. **29**, 1261 (1933).
(6) BAARS: Sitzber. ges. Beförder. Naturw. Marburg **63**, 213 (1928).
(7) BENNETT AND THOMPSON: J. Phys. Chem. **20**, 216 (1916).

(8) Béthune and Kimball: J. Chem. Phys. **13**, 53 (1945).
(9) Bikerman: Phil. Mag. [7] **33**, 384 (1942).
(10) Bircher and Harkins: J. Am. Chem. Soc. **35**, 2890 (1923).
(11) Bockris: Thesis, London, 1945.
(12) Bockris: Nature **158**, 584 (1946).
(13) Bockris: Trans. Faraday Soc. **43**, 417 (1947).
(14) Bockris: Nature **159**, 539 (1947).
(15) Bockris: Faraday Society Discussion on Electrode Processes, 1947, p. 95.
(16) Bockris: In course of publication.
(17) Bockris: Unpublished work.
(18) Bockris and Azzam: Experientia **4**, 92 (1948).
(19) Bockris and Azzam: In course of publication.
(20) Bockris and Conway: Nature **159**, 711 (1947).
(21) Bockris and Conway: J. Sci. Instruments **19A**, 23 (1948).
(22) Bockris and Conway: In course of publication.
(23) Bockris and Ignatowicz: Trans. Faraday Soc. **44**, 519 (1948).
(24) Bockris and Parsons: Trans. Faraday Soc. **44**, (1948) and in course of publication.
(25) Bockris, Parsons, and Conway: In course of publication.
(26) Bonhoeffer: Z. physik. Chem. **113**, 213 (1924).
(27) Bonnemay: Compt. rend. **223**, 76 (1946).
(28) Bowden: Trans. Faraday Soc. **24**, 473 (1928).
(29) Bowden: Proc. Roy. Soc. (London) **A126**, 107 (1929).
(30) Bowden: Trans. Faraday Soc. **31**, 105 (1933).
(31) Bowden and Agar: Ann. Repts. on Progress Chem. (Chem. Soc. London) **35**, 90 (1938).
(32) Bowden and Grew: Faraday Society Discussion on Electrode Processes, 1947.
(33) Bowden and O'Connor: Proc. Roy. Soc. (London) **A128**, 317 (1930).
(34) Bowden and Price: Quoted by Bowden and Agar (31).
(35) Bowden and Rideal: Proc. Roy. Soc. (London) **A120**, 59, 80 (1928).
(36) Bowden and Stout: Quoted by Bowden and Agar (31).
(37) Butler: Proc. Roy Soc. (London) **A157**, 423 (1936).
(38) Butler: J. Chem. Phys. **9**, 279 (1941).
(39) Butler and Armstrong: Trans. Faraday Soc. **29**, 1261 (1933).
(40) Cassel and Krumbein: Z. physik. Chem. **171**, 70 (1934).
(41) Cassel and Salditt: Z. physik. Chem. **155A**, 321 (1931).
(42) Chappell, Roethel, and McCarthy: Ind. Eng. Chem. **20**, 582 (1938).
(43) Cruatto and Da Via: Gazz. chim. ital. **73**, 117 (1943).
(44) Denina: Gazz. chim. ital. **64**, 527 (1934).
(45) Dolin, Erschler, and Frumkin: Acta Physicochim. U.R.S.S. **13**, 779 (1940).
(46) Dolin, Erschler, and Frumkin: J. Phys. Chem. (U.S.S.R.) **14**, 907 (1940).
(47) Drucker: Z. Elektrochem. **33**, 504 (1927).
(48) Eley: Faraday Society Discussion on Electrode Processes, 1947, p. 138.
(49) Erdey-Grúz and Szarvas: Z. physik. Chem. **177**, 277 (1936).
(50) Erdey-Grúz and Volmer: Z. physik. Chem. **150**, 203 (1930).
(51) Erdey-Grúz and Wick: Z. physik. Chem. **162A**, 53 (1932).
(52) Erschler: Acta Physicochim. U.S.S.R. **1**, 327 (1937).
(53) Erschler: Faraday Society Discussion on Electrode Processes, 1947, p. 209.
(54) Erschler, Deborin, and Frumkin: Acta Physicochim. U.R.S.S. **8**, 555 (1938).
(55) Essin: Z. physik. Chem. **166**, 270 (1933).
(56) Essin and Kosheurov: Acta Physicochim. U.R.S.S. **16**, 169 (1942).
(57) Eyring, Glasstone, and Laidler: J. Chem. Phys. **1**, 1053 (1939).
(58) Fedotov: Quoted by Frumkin (72).
(59) Ferguson: Trans. Electrochem. Soc. **76**, 757 (1939).
(60) Ferguson and Bandes: Trans. Electrochem. Soc. **81**, 105 (1942).
(61) Ferguson and Chen: J. Phys. Chem. **39**, 191 (1935).

(62) Ferguson and Dupbernall: Trans. Electrochem. Soc. **64,** 221 (1933).
(63) Ferguson and Kleinhechsel: J. Phys. Chem. **42,** 171 (1938).
(64) Fischer and Barabanov: Bull. sci. Univ. Kiev **2,** 97 (1936).
(65) Fowler: Trans. Faraday Soc. **28,** 368 (1932).
(66) Frumkin: Z. physik. Chem. **164,** 121 (1933).
(67) Frumkin: Acta Physicochim. U.R.S.S. **7,** 474 (1937).
(68) Frumkin: J. Phys. Chem. (U.S.S.R.) **14,** 886 (1940).
(69) Frumkin: Acta Physicochim. U.R.S.S. **12,** 243 (1940).
(70) Frumkin: Sci. Papers Inst. Phys. Chem. Research (Tokyo) **37,** 473 (1940).
(71) Frumkin: Acta Physicochim. U.R.S.S. **18,** 23 (1943).
(72) Frumkin: Faraday Society Discussion on Electrode Processes, 1947, p. 57.
(73) Frumkin and Aladjalowa: Acta Physicochim. U.R.S.S. **19,** 1 (1944).
(74) Frumkin and Proskurnin: Trans. Faraday Soc. **31,** 110 (1935).
(75) Gatty and Spooner: *The Potential Behaviour of Dissolving Metals*, p. 450. University Press, Oxford (1938).
(76) Glasstone: J. Chem. Soc. **125,** 250 (1924).
(77) Glasstone: *Electrochemistry of Solutions*, p. 438. Methuen and Company, Ltd., London (1945).
(78) Gonyi: Ann. phys. [9] **7,** 129 (1917).
(79) Goodeve: Faraday Society Discussion of Electrode Processes, 1947, p. 139.
(80) Goodwin and Wilson: Trans. Electrochem. Soc. **40,** 113 (1921).
(81) Gore: Proc. Roy. Soc. (London) **38,** 209 (1885).
(82) Grant: Trans. Faraday Soc. **24,** 226 (1928).
(83) Gurney: Proc. Roy. Soc. (London) **A134,** 137 (1931).
(84) Hammett: Trans. Faraday Soc. **29,** 770 (1933).
(85) Harkins: Thesis, University of Chicago, 1914.
(86) Harkins and Adams: J. Phys. Chem. **29,** 215 (1925).
(87) Heyrovsky: Collection Czechoslov. Chem. Communs. **9,** 273 (1937).
(88) Hickling: Trans. Faraday Soc. **33,** 1540 (1937).
(89) Hickling: Trans. Faraday Soc. **37,** 352 (1941).
(90) Hickling and Salt: Trans. Faraday Soc. **36,** 1226 (1940).
(91) Hickling and Salt: Trans. Faraday Soc. **37,** 224 (1941).
(92) Hickling and Salt: Trans. Faraday Soc. **37,** 319 (1941).
(93) Hickling and Salt: Trans. Faraday Soc. **37,** 333 (1941).
(94) Hickling and Salt: Trans. Faraday Soc. **37,** 450 (1941).
(95) Hickling and Salt: Trans. Faraday Soc. **38,** 474 (1942).
(96) Hirota and Horiuti: Bull. Chem. Soc. Japan **13,** 228 (1938).
(97) Hoar: Proc. Roy. Soc. (London) **A142,** 628 (1933).
(98) Horiuti and Ikusima: Proc. Imp. Acad. (Tokyo) **15,** 39 (1939).
(99) Horiuti, Okamoto, and Hirota: Sci. Papers Inst. Phys. Chem. Research (Tokyo) **29,** 223 (1936).
(100) Horiuti and Polanyi: Acta Physicochim. U.R.S.S. **2,** 505 (1935).
(101) Ipatiev *et al.*: J. Phys. Chem. (U.S.S.R.) **5,** 1114 (1934).
(102) Jofa: Quoted by Frumkin (71).
(103) Jofa: Acta Physicochim. U.R.S.S. **10,** 903 (1939).
(104) Jofa: J. Phys. Chem. (U.S.S.R.) **19,** 117 (1945).
(105) Jofa and Frumkin: Acta Physicochim. U.R.S.S. **18,** 183 (1943).
(106) Jofa and Kabanov: Acta Physicochim. U.R.S.S. **10,** 616 (1939).
(107) Jofa, Kabanov, Kutchinski, and Chystiakov: Acta Physicochim. U.R.S.S. **10,** 317 (1939).
(108) Jofa and Mikulin: J. Phys. Chem. (U.S.S.R.) **18,** 137 (1944).
(109) Jofa and Stepanova: J. Phys. Chem. (U.S.S.R.) **19,** 125 (1945).
(110) Kabanov: Acta Physicochim. U.R.S.S. **4,** 846 (1936).
(111) Kaminsky: Unpublished work.

(112) KARPEN: Compt. rend. **222**, 541 (1946).
(113) KENYON: Dissertation, Cambridge University, 1937.
(114) KIMBALL, GLASSTONE AND GLASSNER: J. Chem. Phys. **9**, 91 (1941).
(115) KNOBEL: J. Am. Chem. Soc. **46**, 2613 (1924).
(116) KNOBEL, CAPLAN, AND EISEMANN: Trans. Electrochem. Soc. **43**, 55 (1923).
(117) KNORR AND SCHWARTZ: Z. physik. Chem. **176**, 161 (1936).
(118) KOBOZEV AND NEKRASOV: Z. Elektrochem. **36**, 529 (1930).
(119) KOLOTYRKIN AND BUNE: J. Phys. Chem. (U.S.S.R.) **21**, 581 (1947).
(120) LEGRAN AND LEVINA: Acta Physicochim. U.R.S.S. **12**, 243 (1940).
(121) LEGRAN AND LEVINA: J. Phys. Chem. (U.S.S.R.) **14**, 211 (1940).
(122) LEMARCHANDS AND JUDA: Compt. rend. **207**, 1192 (1938).
(123) LEVINA AND SARINSKY: Acta Physicochim. U.R.S.S. **6**, 491 (1937).
(124) LEVINA AND SILBERFARB: Acta Physicochim. U.R.S.S. **4**, 282 (1936).
(125) LUGGIN: Z. physik. Chem. **32**, 208 (1900).
(126) LUKOVTSEV: J. Phys. Chem. (U.S.S.R.) **21**, 589 (1947).
(127) LUKOVTSEV, LEVINA, AND FRUMKIN: Acta Physicochim. U.R.S.S. **11**, 21 (1939).
(128) MARIE AND LEJEUNE: Compt. rend. **179**, 679 (1924).
(129) MITUYA: Bull. Inst. Phys. Chem. Research (Tokyo) **19**, 142 (1940).
(130) NERNST AND LESSING: Nachr. kgl. Ges. Wiss. Göttingen **1902**, 54.
(131) NEWBERY: J. Chem. Soc. **105**, 2422 (1914).
(132) NEWBERY: Trans Faraday Soc. **43**, 136 (1947).
(133) NORIGUCHI: J. Chem. Soc. Japan **55**, 749 (1934).
(134) NOVOSELSKI: J. Phys. Chem. (U.S.S.R.) **11**, 369 (1938).
(135) OKAMOTO, HORIUTI, AND HIROTA: Sci. Papers Inst. Phys. Chem. Research (Tokyo) **29**, 223 (1936).
(136) PARSONS: Thesis, London, 1948.
(137) PHOMOTOV: Trudy Moskov. Khim. Tekhnol. Inst. im. D.I. Mendeleeva **No. 6**, 127 (1940).
(138) PIONTELLI: Atti accad. naz. Lincei, Clàsse sci. fis. mat. e nat. **27**, 581 (1938).
(139) PLESKOV: Acta Physicochim. U.R.S.S. **11**, 305 (1939).
(140) PORFIROV: Compt. rend. acad. sci. U.R.S.S. **1**, 386 (1935).
(141) PRING AND TAINTON: J. Chem. Soc. **105**, 722 (1914).
(142) ROITER AND JAMPOLSKAJA: Acta Physicochim. U.R.S.S. **7**, 247 (1937).
(143) SAND, LLOYD, AND GRANT: J. Chem. Soc. **1927**, 328.
(144) SCHAAP: Z. physik. Chem. **268**, 413 (1934).
(145) SCHMIDT AND STOLL: Z. Elektrochem. **47**, 316 (1941).
(146) SEDERHOLM AND BENEDICKS: Z. Elektrochem. **38**, 77 (1932).
(147) SEMERANO: Gazz. chim. ital. **63**, 706 (1933).
(148) SINDJUKOV: Thesis, Moscow, 1947.
(149) SMITS: *The Theory of Allotropy*, p. 115. Longmans, Green and Company, London (1922).
(150) STERN: Z. Electrochem. **30**, 508 (1924).
(151) STOUT: Trans. Faraday Soc. **41**, 64 (1945).
(152) STOUT: Faraday Society Discussion on Electrode Processes, 1947, pp. 107, 246.
(153) TAFEL: Z. physik. Chem. **50**, 641 (1905).
(154) TOPLEY AND EYRING: Nature **133**, 292 (1934) (details of calculations unpublished).
(155) UHLIG, CARR, AND SCHNEIDER: Z. Elektrochem. **79**, 111 (1941).
(156) VARISIKOVA AND KABANOV: J. Phys. Chem. (U.S.S.R.) **14**, 1620 (1940).
(157) VOLMER AND WICK: Z. physik. Chem. **172**, 429 (1935).
(158) See reference 157.
(159) VON NARAY-SZABO: Z. Elektrochem. **31**, 95 (1925).
(160) VON NARAY-SZABO: Naturwissenschaften **25**, 12 (1937).
(161) VON NARAY-SZABO: Z. physik. Chem. **137**, 355 (1937).
(162) WIRTZ: Z. Elektrochem. **44**, 303 (1938).